

**Official Title:** NATIONAL PHASE IIIB PROSPECTIVE , TWO-COHORT NON-RANDOMIZED, MULTI-CENTRE, OPEN LABEL STUDY TO ASSESS THE SAFETY OF SUBCUTANEOUS TRASTUZUMAB AND MOLECULAR BIOMARKERS IN PATIENTS WITH EARLY AND LOCALLY ADVANCED HER2-POSITIVE BREAST CANCER

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## PROTOCOL

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**TEST PRODUCT:** Trastuzumab SC (RO 4

**MEDICAL MONITOR:** Dr. [REDACTED]

**PRINCIPAL INVESTIGATOR:** Dr. [REDACTED]

**STATISTICIAN:** Dr. [REDACTED]

**SPONSOR:** Roche S.p.A

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## PROTOCOL ACCEPTANCE FORM

**TITLE:** NATIONAL PHASE IIIB PROSPECTIVE, TWO-COHORT NON-RANDOMIZED, MULTI-CENTRE, OPEN LABEL STUDY TO ASSESS THE SAFETY OF SUBCUTANEOUS TRASTUZUMAB AND MOLECULAR BIOMARKERS IN PATIENTS WITH EARLY AND LOCALLY ADVANCED HER2-POSITIVE BREAST CANCER

**PROTOCOL NUMBER:** ML28879

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**EUDRACT NUMBER:** 2013-001161-16

**IND NUMBER:** Not Applicable

**TEST PRODUCT:** Trastuzumab SC (RO 45-2317)

**MEDICAL MONITOR:** Dr. [REDACTED]

**STATISTICIAN:** Dr, [REDACTED]

**PRINCIPAL INVESTIGATOR:** Dr. [REDACTED]

**SPONSOR:** Roche S.p.A

I agree to conduct the study in accordance with the current protocol.

---

Principal Investigator's Name (print)

---

Principal Investigator's Signature

---

Date

Please return a copy of the form as instructed by your local study monitor. Please retain the original for your study files.

## PROTOCOL SYNOPSIS

<b>TITLE:</b>	<b>NATIONAL PHASE IIIB PROSPECTIVE, TWO-COHORT NON-RANDOMIZED, MULTI-CENTRE, OPEN LABEL STUDY TO ASSESS THE SAFETY OF SUBCUTANEOUS TRASTUZUMAB AND MOLECULAR BIOMARKERS IN PATIENTS WITH EARLY AND LOCALLY ADVANCED HER2-POSITIVE BREAST CANCER</b>
<b>PROTOCOL NUMBER:</b>	<b>ML28879</b>
<b>EUDRACT NUMBER:</b>	2013-001161-16
<b>IND NUMBER:</b>	Not Applicable
<b>TEST PRODUCT:</b>	Trastuzumab SC (RO 45-2317)
<b>PHASE:</b>	IIb
<b>INDICATION:</b>	Early and locally advanced breast cancer
<b>SPONSOR:</b>	Roche S.p.A

This study is a part (Daughter study) of Global (Umbrella) Study. An open-label, multinational, multicenter phase IIIB study with subcutaneous administration of trastuzumab in patients with HER2 positive early breast cancer or metastatic breast cancer.

### **Objectives**

#### **Primary Objective**

The primary objective of the study is to assess the safety and tolerability of trastuzumab solution injected subcutaneously (vial or single-use injection device [SID]) in patients with HER2-positive early breast cancer (eBC) or locally advanced breast cancer (LABC)

#### **Secondary Objectives**

The secondary objectives for this study are the following:

- Exposure to study medication
- Duration of treatment, follow-up, and safety observation
- Efficacy:
  - disease-free survival ( DFS), overall survival (OS)

- In the Neo-adjuvant setting activity of two sequential drug regimens, Anthracycline-containing regimen followed by concomitant administration of Taxane and Trastuzumab SC, assessed as the incidence of pathological Complete Response in breast and nodes (pCR; ypT0-is ypN0)
- Patient Satisfaction using SID (single use injection device)
- HCP satisfaction

### **Explorative Secondary Objective**

The exploratory secondary objective of the local study is the assessment of PI3K mutation in tumor tissues and in circulating free DNA (cfDNA) in blood.

These assessments will be performed:

- to evaluate the agreement between the PI3K mutation assessment in tumor tissue (gold standard) and in circulating free DNA (experimental)
- to correlate the baseline mutation status (in tumor tissue and cfDNA) with clinical outcome (pathological response to treatment in the neoadjuvant arm)
- to correlate the pharmacodynamic change of the cfDNA before and **after treatment with clinical outcome.**

Local safety and efficacy data will be transferred to a global Umbrella database and will be pooled for analysis. These data will also be analyzed in subgroups according to study design, patient population, and other relevant factors.

## **Study Design**

### **Description of the Study**

This is a prospective, two-cohort, non-randomized, multicenter, open-label study to assess the safety and tolerability of trastuzumab solution injected subcutaneously (vial or single-use injection device [SID]) in approximately 240 patients with HER2-positive eBC or LABC who are eligible for anti-HER2 therapy.

The patients will be enrolled in two sequential cohorts.

The first 120 patients will be treated with trastuzumab SC 600 mg/5ml vial (Cohort A) and the subsequent 120 patients will be treated with trastuzumab SC 600 mg/5ml prefilled single use injection device - SID (Cohort B).

In each cohort (A and B), patients will be allocated to adjuvant or neoadjuvant treatment, with pragmatic selection according to conventional clinical criteria and physician choice:

- Group 1 = Adjuvant chemotherapy + trastuzumab SC
- Group 2= Neoadjuvant chemotherapy + trastuzumab SC

In both groups the planned treatment will require sequential chemotherapy regimens containing 4 cycles of Anthracyclines followed by 4 cycles of Taxanes based chemotherapy administered in combination with trastuzumab SC followed by trastuzumab alone.

The following additional criteria must be satisfied:

Concomitant trastuzumab SC 600mg administered subcutaneously using either a handheld syringe or SID, starting after Anthracyclines comprehensive sequences.

The therapy should include a total of 18 cycles/1 year of trastuzumab SC.

Doxorubicin cumulative doses  $\leq 300$  mg/m<sup>2</sup> or equivalent for Epirubicin.

Chemotherapy treatment duration, either in the Adjuvant or in the neoadjuvant group, of 8 total cycles.

The whole neoadjuvant chemotherapy must be given before surgery.

Surgery after neoadjuvant chemotherapy + trastuzumab SC should include conventional surgical procedures on the breast and on the axilla. SNB (Sentinel lymph node biopsy) is consented in patients with clinically negative axillary status at starting treatment.

Postoperative RT and/or hormonal treatment can be administered concomitantly with trastuzumab SC as adjuvant treatment after chemotherapy, when indicated.

With the purpose of fertility preservation, for adjuvant patients only, LH-RH analogous administration is allowed without any limitation.

The following sequential chemotherapy regimens are allowed, for the Adjuvant and Neoadjuvant subsets:

- AC/EC, 4 cycles (cycles A1 to A4) → weekly Paclitaxel, 12 wks
- AC/EC, 4 cycles (cycles A1 to A4) → Docetaxel, 4 cycles
- FAC/FEC, 4 cycles (cycles A1 to A4) → weekly Paclitaxel, 12 wks
- FAC/FEC, 4 cycles (cycles A1 to A4) → Docetaxel, 4 cycles.

Adjuvant chemotherapy should start within 10 weeks from definite surgery.

Primary chemotherapy with Anthracyclines should start as soon as possible after study inclusion and no later than 5 working days.

Tissues samples from diagnostic core biopsy and from surgical specimens, as well as blood samples at the planned time points should be collected as reported in Appendix 1.

The centralization of biological materials (tissues and blood) is a definite prerequisite for the study for the evaluation of PI3K mutations, as well the centralized re-evaluation of HER2 positivity on tissues. The results of HER2 positivity performed centrally will not be required prior to the enrollment into the study.

Safety and efficacy data (DFS and OS) collected in this local study will be transferred to a global Umbrella database for a pooled analysis.

The schedules of mandatory clinical assessments for patients with eBC and for patients with LABC are provided in Appendix 1.

### **Number of Patients**

This study will recruit 240 total patients (eBC and LABC).

### **Target Population**

Patients must meet the following criteria for study entry:

#### **Inclusion Criteria:**

To be eligible for the study, a patient must fulfill each of the following criteria:

1. Female and male patients aged  $\geq 18$  years
2. Signed informed consent before any specific study procedure
3. Able and willing to comply with protocol
4. Eastern Cooperative Oncology Group (ECOG) performance status 0–1
5. HER2-positive disease immunohistochemistry (IHC) 3+ or in situ hybridization (ISH) positive, as determined in a local laboratory that is experienced/certified in HER2-expression testing using an accurate and validated assay
6. Histologically confirmed non-metastatic primary invasive adenocarcinoma of the breast. Stage of disease: T1-4, N0-3, M0.  
pT1a-b and pTmic may be included in the presence of at least one of the following unfavorable prognostic factors:
  - clinical( concomitant axillary involvement)and/or
  - biological (negative hormonal receptor status and/or high tumor grade and/or young age and/or lymph/vascular invasion and/or high Ki-67)
7. Left ventricular ejection fraction (LVEF) of  $\geq 55\%$  measured by echocardiography (ECHO) or multiple gated acquisition (MUGA) scan prior to first dose of trastuzumab SC
8. Availability of formalin–fixed paraffin-embedded (FFPE) tissue block or partial block from diagnostic core biopsy (only neoadjuvant patients) and from surgical specimens (both adjuvant and neoadjuvant patients), with representative invasive part of the tumor for additional biomarker analysis
9. Intact skin at site of SC injection on the thigh

## Exclusion Criteria

1. History of other malignancy which could affect compliance with the protocol or interpretation of results. Patients with curatively treated carcinoma in situ of the cervix or basal cell carcinoma, and patients with other curatively treated malignancies, other than breast cancer, who have been disease-free for at least 5 years, are eligible
2. Severe dyspnea at rest or requiring supplementary oxygen therapy
3. Concurrent serious diseases that may interfere with planned treatment, including severe pulmonary conditions/illness
4. Serious cardiac illness or medical conditions that would preclude the use of trastuzumab, specifically: history of documented congestive heart failure (CHF), high-risk uncontrolled arrhythmias, angina pectoris requiring medication, clinically significant valvular disease, evidence of transmural infarction on electrocardiogram (ECG), diagnosed poorly controlled hypertension
5. Known infection with human immunodeficiency virus (HIV), active hepatitis B virus (HBV) or hepatitis C virus (HCV)
6. Pregnant or lactating women. Positive serum pregnancy test in women of childbearing potential, premenopausal or less than 12 months of amenorrhea post-menopause, within 7 days prior to the first administration of the protocol required chemotherapy treatment
7. Women of childbearing potential, premenopausal or less than 12 months of amenorrhea post-menopause (unless surgically sterile), and male patients with partners of childbearing potential who are unable or unwilling to use adequate contraceptive measures during study treatment. In this study, menopause is defined as a minimum of 12 consecutive months of amenorrhea during which time no other biological or physiological cause had been identified as a potential cause of this state. Examples of adequate contraceptive measures are intrauterine device, barrier method (condoms, diaphragm) also in conjunction with spermicidal jelly, or total abstinence. Oral, injectable, or implant hormonal contraceptives are not acceptable
8. Concurrent enrolment in another clinical trial using an investigational anti-cancer treatment, including hormonal therapy, bisphosphonate therapy and immunotherapy, within 28 days prior to the first dose of study treatment
9. Known hypersensitivity to trastuzumab, murine proteins, to any of the excipients of Herceptin® including hyaluronidase, or the adhesive of the SC device (for cohort B), or a history of severe allergic or immunological reactions, e.g. difficulty to control asthma
10. No compliance or adherence with the requirements of the protocol
11. Inadequate bone marrow function (as indicated by any of the following):
  - a) Absolute neutrophil count (ANC)  $< 1,500 / \text{mm}^3$  ( $< 1.5 \times 10^9/\text{L}$ )
  - b) Platelets  $< 100,000 / \text{mm}^3$  ( $< 100 \times 10^9/\text{L}$ )
  - c) Hemoglobin  $< 10 \text{ g/dL}$
12. Impaired hepatic function (as indicated by any of the following):

- a) Serum total bilirubin  $> 1.5 \times$  upper limit of normal (ULN)
- b) Alanine amino transferase (ALT) and/or aspartate amino transferase (AST)  $> 2.5 \times$  ULN
- c) Alkaline phosphatase (ALP)  $> 2.5 \times$  ULN
- 13. Inadequate renal function, as indicated by serum creatinine  $> 1.5 \times$  ULN
- 14. Hormonal treatment concomitant with chemotherapy (allowed in adjuvant phase with adjuvant Trastuzumab SC.)
- 15. Pre-existing motor or sensory neuropathy of Grade  $> 1$
- 16. Sincronous bilateral invasive breast cancer

### **Length of Study**

The study is estimated to last 5 years from the enrollment of the first patient (18 months of recruitment 15 months of study treatment and 2 years of follow-up)

### **Treatment Duration**

eBC and LABC patients will be treated with trastuzumab for a total of 18 cycles/1 year, unless intolerable toxicity or investigator-assessed disease progression occurs or the patient withdraws consent.

### **Safety Follow-up**

All patients will be followed up for 24 months after the last patient has received his/her last study treatment, or earlier, if one of the following is documented: withdrawal from the study, loss to follow-up or death.

### **End of Study**

Last patient last visit (LPLV) in the follow-up period

### **Centers**

A total of 60 oncological centers in Italy will be selected

### **Safety Outcome Measures**

Adverse event (AE) collection will be the primary endpoint for this study. Summaries to be produced will include:

- Incidence and severity by NCI CTCAE version 4.0 of AEs and serious adverse events (SAEs)
- AEs leading to premature discontinuation of study treatment
- Cardiac safety
- Cardiac AEs
  - CHF (according to NCI CTCAE version 4.0 and New York Heart Association [NYHA] Classification)
  - LVEF over time. In the event of an asymptomatic decline in LVEF, an algorithm (Appendix 2 in the protocol) will be used to determine whether to continue trastuzumab SC treatment
- Secondary safety assessments will include the following:
  - Exposure to study medication



- Duration of treatment, follow-up, and safety observation
- ECOG
- Concomitant medications
- Laboratory data, vital signs and physical examination
- Premature withdrawals and major protocol violations

The primary analysis will be for all patients in the Safety population.

### **Efficacy Outcome Measures**

The efficacy outcome measures of this study will be to collect data for subcutaneous administration of trastuzumab in the treatment of HER2-positive eBC and LABC:

- DFS
- OS

Diagnosis of breast cancer relapse will be made based on routine clinical, radiological and laboratory criteria. In case of uncertainty, disease progression should be confirmed by histological or cytological examination of a suspicious lesion, if possible.

In the Neo-adjuvant setting, the activity of two sequential drug regimens, Anthracycline-containing regimen followed by concomitant administration of Taxane and Trastuzumab SC, will be assessed as:

- the incidence of pathological Complete Response in breast and nodes (pCR) (ypT0-is ypN0). Residual in situ disease (ypTis) is considered as pCR.

### **Physician/Patient-Satisfaction Outcome Measures**

Patient Satisfaction will be assessed by Patient Satisfaction Questionnaire only in Cohort B (use of Trastuzumab SC SID).

In Cohort B, a questionnaire will be completed by patients able to use SID, who completed a minimum of 14 administrations of trastuzumab SC using SID (at least 10 self-administered).

Health Care Professional (HCP) satisfaction will be assessed by a Health Care Professional Questionnaire (HCPQ). A questionnaire will be completed by both the Investigator and a study nurse at each site when at least 4 patients from their site have received at least 5 cycles of adjuvant study treatment. (For sites that recruit <4 patients, the investigator and a study nurse will each complete an HCPQ when the last patient at their site has received at least 5 cycles of adjuvant study treatment).

### **Translational study**

The assessment of PI3K mutations will be performed at baseline in tumor tissues (core biopsy and tumor block for neoadjuvant patients; tumor block for adjuvant patients) and both at baseline (before starting anthracycline treatment) pre- and post- SC trastuzumab-chemotherapy combination in blood derived circulating free DNA (cfDNA).

A comparison between PI3K mutation assessment in tumor tissue collected at baseline (core biopsy and tumor block for neoadjuvant patients; tumor block for adjuvant patients) (gold standard assessment) and the assessment of PI3K mutation in cfDNA (experimental assessment) will be performed.

Sensitivity, specificity, positive and negative predictive value and overall agreement for the experimental assessment will be calculated.

Correlative studies will be performed according to the following clinical outcome:

- the achievement of pathological complete response (pCR) of invasive tumor in breast and axilla (in situ residual disease allowed). Patients progressed under treatment or for which surgery will not be feasible at the end of treatment will be considered as not having achieved a pCR. The association between clinical outcomes (pCR) and the baseline assessment of the PI3K mutation status as defined in tumor samples or cfDNA, will be performed.

The pharmacodynamic changes of the PI3K mutation assessment in cfDNA by comparing the baseline and after treatment evaluation will be defined. Moreover a correlation between these pharmacodynamic changes and clinical outcome (pCR) will be performed.

### **Investigational Medicinal Products**

Trastuzumab SC (vial and SID) will be considered as an Investigational Medicinal Product (IMP) in this study.

Trastuzumab SC will be administered subcutaneously with a fixed dose of 600 mg (irrespective of body weight) throughout the study treatment q3wks for 1 year. Concurrent complementary radiotherapy and adjuvant hormonal therapy will be allowed as per institutional guidelines.

Trastuzumab SC will be supplied as a vial for manual administration via hand-held syringe (Cohort A) or SID (Cohort B). With either method, trastuzumab will be subcutaneously injected slowly over a period of up to 5 minutes.

**Vial:** ready to use solution (600 mg trastuzumab/5 ml) for manual administration using a hand-held syringe

**SID:** a ready-to-use automated injection device containing 600 mg/5 ml trastuzumab

Administration using a hand-held syringe must be performed by HCP. SID might be administered in the hospital by HCP or self-administration. For self-administration, patients must have been trained by HCP. Once adequately trained, patients should be asked to self-administer the drug under the supervision of the HCP.

### **Comparator**

Not applicable.

### **Non-Investigational Medicinal Products**

Chemotherapy regimen inclusive of Anthracyclines and Taxanes for 8 cycles, considered as non investigational Medicinal Product, (adjuvant and neoadjuvant) will be administered in accordance with the local prescribing information. Doses will be calculated for all drugs according to the patient's body surface area (BSA). In calculating BSA, actual weights should be used.

The following combination therapies may be used with trastuzumab SC according to local approved regimen:

- AC/EC, 4 cycles → weekly Paclitaxel, 12 wks
- AC/EC, 4 cycles → Docetaxel, 4 cycles
- FAC/FEC, 4 cycles → weekly Paclitaxel, 12 wks
- FAC/FEC, 4 cycles → Docetaxel, 4 cycles

Chemotherapy should be administered following trastuzumab SC injection, and as per local Product Information and the investigator's discretion.

Hormonal therapy and complementary radiotherapy can be administered concurrently, as adjuvant after chemotherapy, according to local guidelines.

### **Procedures (summary)**

The complete schedule of assessment is provided in Appendix 1 of the protocol.

Collected tumor tissues and blood samples in both subsets will be centrally analyzed at the end of treatment of the last included patient.

The analysis of PI3K mutation on tissues and on serum cfDNA, as well the centralized re-evaluation of HER2-positivity on tissues will be performed for care of the laboratories of [REDACTED].

The results of HER 2 positivity performed centrally will not be required prior to the enrollment into the study.

Moreover, the patients will be proposed to donate the remnants of biological samples for future biomarker researches, to the [REDACTED]. The biological samples will be stored in the [REDACTED], under the supervision and responsibility of the [REDACTED].

### **Statistical Methods**

The Safety population will be defined as all enrolled patients who received at least one dose of study medication. All summaries of safety data will be based on the Safety population.

The Intent-to-Treat (ITT) population will be defined as all enrolled patients. The modified-Intent-to-Treat (m-ITT) population will be defined as all enrolled

patients satisfying inclusion and exclusion criteria for eligibility. All baseline summaries will be based on the ITT, while efficacy analyses will be based on the m-ITT population.

### **Primary Analysis**

The primary analysis of the safety endpoints will be undertaken once all patients have completed the study (treatment phase and safety follow-up (4 weeks after their last dose of study treatment)).

The incidence of AEs and SAEs will be summarized according to the primary system-organ class (SOC) and within each SOC, by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term.

Analysis will focus on incidence of AEs and SAEs, AEs leading to premature discontinuation of study treatment, specific cardiac AEs and SAEs and summaries of LVEF. Summaries will include frequency counts and percentages. For certain AEs (or groups of AEs), e.g. cardiac AEs, 95% confidence intervals (calculated using Clopper-Pearson methodology) for incidences will be provided.

### **Secondary Analysis**

Secondary safety parameters include exposure to study medication, duration of treatment and follow-up, vital signs, weight, height, ECOG, concomitant medications, laboratory parameters, premature withdrawals, and major protocol violations.

Secondary efficacy endpoint for Neo-adjuvant setting will be pCR.

According to the literature data, the expected rate of pCR will be about 35-40%. (Gianni L, 2008). Response rate will be presented as proportion with relative 95% confidence intervals.

Secondary efficacy endpoints for eBC and LABC are also DFS and OS.

DFS is defined as the time from baseline visit until first documented disease or death, whichever comes first. Patients who have no disease and have not died or who are lost to follow-up at the time of analysis will be censored at the date of the last tumor assessment where no disease was documented or the last date of follow-up for disease, whichever is last. Patients without post baseline tumor assessments will be censored at the time of their baseline visit unless death occurs prior to their first scheduled tumor assessment.

OS is defined as the time from baseline visit until death from any cause. Patients still alive at the time of analysis and patients who are lost to follow-up will be censored at their last time known to be alive.

The OS and DFS experience will be estimated using Kaplan-Meier methodology and summarized using, the 25<sup>th</sup> and 75<sup>th</sup> percentiles, the median and a 95% confidence interval for the median. The plot of Kaplan-Meier estimates for the single treatment group will be presented.

Data derived from the questionnaires regarding patients' satisfaction and HCP satisfaction will be also presented as proportion with relative 95% confidence intervals.

### **Exploratory Analysis**

For the analysis of translational study, the association of PI3K mutation status at baseline and pCR (neoadjuvant arm) will be assessed by means of a univariate and multivariate logistic regression analysis, where the odds of pCR will be modeled as function of the marker and adjusted by baseline factors relative to tumor and patients characteristics. The association between the pharmacodynamic change of the assessment for the PI3K mutation status in cfDNA pre- and post- treatment and pCR will be performed as described above. The cut-off value for statistical significance will be set =0.05 two tails.

***The analysis of efficacy secondary end points will be conducted according to local and to central HER2 evaluation, while the translational evaluations will be conducted only on the central HER2 positive cases.***

All analyses will be described on the overall population of interest and broken down by relevant characteristics of patients and disease, where deemed appropriate.

### **Interim Analyses**

The primary analysis will be undertaken once all patients have completed the study (treatment phase and 28-days safety follow-up visit). In addition to this primary analysis there will be annual interim analysis for safety reporting and presentation of safety and efficacy results. These annual reporting events will start 1 year after first visit and end when the last patient has finished follow-up

### **Determination of Study Sample Size**

The study focuses on a sample of patients eligible for adjuvant and neoadjuvant chemotherapy+ trastuzumab SC.

Patients will receive treatment according to the following schema, which is usually adopted in clinical practice.

- Neoadjuvant: CT x 4 cycles (Cycles A1 to A4)→CT+Trastuzumab SC x 4 cycles (Cycles 1 to 4)→ Surgery → Trastuzumab SC x 14 cycles (Cycles 5 to 18)
- Adjuvant: Surgery → CT x 4 cycles (Cycles A1 to A4)→CT+Trastuzumab SC x 4 cycles (Cycles 1 to 4) → Trastuzumab SC x 14 cycles (Cycles 5 to 18)

Since the chemotherapy amount of treatment is expected to be the same in the two groups, it is reasonable to expect the same incidence of side effects.

For the purpose of the estimation of the sample size, the LVEF rate has been chosen as the safety endpoint of primary interest. The tables provide the resultant confidence intervals for various sample sizes and various event rates, according to the assumptions derived by NOAH study (Gianni et al, Lancet 2010). Assuming an observed LVEF Grade $\geq$  1 rate of 25%, a LVEF Grade $\geq$ 2 of 4% and a LVEF Grade $\geq$ 3 of 2% a sample size of 240 will produce a 95% confidence interval deemed sufficiently precise to draw valid conclusions around the event rate. Safety results within each treatment group will be useful for descriptive purpose. The estimation of the confidence intervals will be performed using SAS based on Clopper-Pearson methodology.

Clopper-Pearson 95% Confidence Intervals for the incidence of different LVEF Grade			
	LVEF Grade: estimated incidence		
Number of Patients	$\geq$ 3: 2%	$\geq$ 2: 4%	$\geq$ 1: 25%
50	0.1% - 10.6%	0.5% - 13.7%	14.6% - 40.3%
190	0.6% - 5.3%	1.8% - 8.1%	19.3% - 32.1%
240	0.7% - 4.8%	2.0% - 7.5%	19.7% - 31.0%

## **LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS**

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
BC	breast cancer
BUN	blood urea nitrogen
CHF	congestive heart failure
CI	confidence interval
C <sub>max</sub>	maximum concentration
CNS	central nervous system
CRO	contract research organization
CT	computed tomography
CTCAE	common terminology criteria for adverse events
DCIS	ductal carcinoma in situ
DLT	dose-limiting toxicity
DoR	duration of response
eBC	early breast cancer
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EEA	European economic area
EGRF	epidermal growth factor receptor
EU	European Union
FDA	Food and Drug Administration

Hb	Hemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIV	immunodeficiency virus
HCP	health care professional
HR	hazard ratio
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug (application)
INR	international normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion-related reaction
ISH	in situ hybridization
ITT	intent-to-treat
IV	Intravenous
LABC	Locally Advanced Early Breast Cancer
LVEF	left ventricular ejection fraction
LPLV	last patient, last visit
mBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MR	Medical Responsible
MRI	magnetic resonance imaging
m-ITT	modified intent-to-treat
MUGA	multiple-gated acquisition
NCI	National Cancer Institute
NYHA	New York Heart Association
ORR	overall response rate
OS	overall survival



pCR	pathological complete response
PD	progressive disease
PET	positron emission tomography
PFS	progression free survival
PK	Pharmacokinetic
PR	partial response
PRO	patient-reported outcome
q3w	every 3 weeks
Qw	Weekly
RECIST	response evaluation criteria for solid tumors
rHuPH20	recombinant humanized hyaluronidase
SAE	serious adverse event
SC	Subcutaneous
SD	standard deviation
SID	single-use injection device
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	system-organ class
STIAMP	Suspected Transmission of Infectious Agents via a Medicinal Product
ULN	upper limit of normal
WBC	white blood cells
WHO	World Health Organization

## **1. BACKGROUND**

### **1.1 BACKGROUND ON BREAST CANCER**

Breast cancer (BC) is the most common cancer in women (23% of all cancers), with a global prevalence of more than 1 million patients and an annual mortality rate of approximately 450,000 deaths (American Cancer Society). In Europe and the USA, most BCs are diagnosed when the cancer is still confined to the breast, with or without loco-regional lymph node spread, and can be treated with curative intent. In Europe, around 79% are potentially operable (stage T1-3N0/+M0), 7% are locally advanced (T4NxM0), and 6% are metastatic (M1) at diagnosis (Sant et al. 2003). However, BC remains a major cause of death in women aged between 35 and 59 years.

#### **1.1.1 TREATMENT OPTIONS FOR eBC**

Surgery is the main modality of local treatment for early breast cancer (eBC) and (with or without radiotherapy) can control loco-regional disease in the majority of patients. However, a significant percentage of patients relapse after loco-regional treatment and develop metastases. Systemic chemotherapy or endocrine therapy in hormone receptor-positive patients reduce the risk of relapse and are given either prior to surgery (neoadjuvant therapy) or following surgery (adjuvant therapy). In recent decades, the use of adjuvant systemic therapies eBC has increased extensively and has most likely contributed to the substantial decline in BC mortality observed in the U.S. and in some European countries (Verma et al. 2010; Colozza et al. 2006, Ferlay et al. 2007).

In the last few years, there has been accelerated progress in the treatment of eBC, with the introduction of taxanes and aromatase inhibitors, and, most impressively, trastuzumab to the adjuvant portfolio (Colozza et al. 2006). Cytotoxic chemotherapy, endocrine therapy, radiotherapy, and molecular targeted therapies currently represent the backbone of modern systemic BC treatment. Several targeted drugs with different molecular pathways have received approval for metastatic breast cancer (mBC), but trastuzumab is the only such therapy that is currently approved for adjuvant or neoadjuvant treatment of eBC (Untch 2010). The use of trastuzumab in the adjuvant setting is also supported by international treatment guidelines for women with HER2-positive BC (NCCN 2012; Gnant et al. 2011; Aebi et al. 2011). The introduction of trastuzumab last decade has particularly improved the outcome for eBC patients with HER2-positive disease.

## 1.2 BACKGROUND ON STUDY TREATMENTS

### 1.2.1 HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR (HER)

The human epidermal growth factor receptor 2 (HER2, HER2/neu, c-erbB-2) gene, first discovered in 1984 (Schechter et al. 1984), is localized to chromosome 17q and encodes a transmembrane tyrosine kinase receptor protein that is a member of the epidermal growth factor receptor (EGFR), or HER, family (Ross et al. 2009). This HER family of four receptors mediates the growth, differentiation and survival of cells (Sundaresan et al. 1999; Yarden and Sliwkowski 2001; Gschwind et al. 2004). The evidence that increased expression and activity of HER2 induces cell transformation and tumorigenesis is overwhelming. In BC, unlike a variety of other epithelial malignancies, HER2 gene amplification is uniformly associated with HER2 (p185neu) protein overexpression.

HER2 gene amplification and/or protein overexpression has been associated with aggressive tumor behaviour, including increased cell proliferation, cell motility, tumor invasiveness, progressive regional and distant metastases, accelerated angiogenesis, and reduced apoptosis and poor prognosis (Ross et al. 2009; Slamon et al. 1987; Slamon et al. 1989; Sjögren et al. 1998; Moasser 2007; Ménard et al. 2001). A review of 107 studies involving 39,730 BC patients found that in the majority (88%) of the studies, either HER2 gene amplification or HER2 (p185neu) protein overexpression predicted BC outcome by either univariate or multivariate analysis (Ross et al. 2009). The frequency of HER2-positivity in these studies ranged from 9% to 74% (mean 22.2%). However, in current practice, most investigators report that the true HER2-positive rate is in the range of 15%–20% (Ross et al. 2009; Lund et al. 2010). The major slide-based HER2 testing approaches include immunohistochemistry (IHC), fluorescence in situ hybridization, and chromogenic in situ hybridization.

HER2 amplified BCs comprise a specific disease subset with a unique molecular portrait and biologic characteristics that distinguish them from other types of BCs (Moasser 2007; Crowe et al. 2006). Studies have shown that women whose tumors exhibit either amplification of the HER2 gene or overexpression of its encoded protein have a more aggressive form of BC that is associated with significantly shortened disease-free and overall survival (OS) compared with women whose tumors do not over express HER2 (Dawood et al. 2010).

Evidence indicates that dysregulation of ligands and receptors of the HER family are important in the pathogenesis of cancer. HER receptors normally exist as inactive monomers. Activation of HER receptors occurs following ligand binding, leading to receptor dimerization and cell signaling through the PI3-kinase/AKT pathway for promotion of tumor cell survival and through the mitogen-activated protein kinase pathway for cellular proliferation. Overexpression of HER2 in BC has been correlated with high histological

grade, increased mitotic activity, p53 mutation, negative estrogen receptor (ER) status, absence of bcl2, and absence of lobular architecture. Despite associations with other known negative prognostic factors, HER2 overexpression has been independently associated with poorer disease-free survival (DFS) and OS compared with tumors that do not overexpress HER2 (Pauletti et al. 2000, Ménard et al. 2001). Approximately 65% of BCs are ER-positive and progesterone receptor-positive (American Cancer Society).

Until the advent of HER2-targeted agents, patients who had HER2-positive eBC faced a markedly poorer prognosis, including reduced relapse-free and OS, than patients with HER2-negative eBC (Ménard et al. 2001; Ross et al. 1998).

### 1.2.2 TRASTUZUMAB (RHUMAB HER2, HERCEPTIN®)

Trastuzumab is a humanized monoclonal antibody directed against the extracellular domain of HER2. It is indicated for the treatment of patients with HER2-positive mBC (first approved in 1998), eBC (approved in 2005), LABC (approved in 2011) and HER2-positive metastatic gastric cancer (approved in 2010). Since its initial approval in 1998, trastuzumab has become standard of care for patients with HER2-positive BC and is widely used for its approved indications in the adjuvant, neoadjuvant and metastatic settings (Ross et al. 2009; NCCN 2012; Gnant et al. 2011; Aebi et al. 2011).

The addition of trastuzumab to standard chemotherapy increases time to progressive disease or the length of progression-free survival (PFS), and improves survival when given with chemotherapy to women with HER2-positive BC (Romond et al. 2005; Slamon et al. 2001). Clinical benefits are greatest in patients with tumors strongly overexpressing HER2, graded 3+ by IHC, and/or with HER2 gene amplification (see Herceptin® Summary of Product Characteristics, 2006).

A randomized Phase II study evaluated trastuzumab and docetaxel vs. docetaxel alone as a first-line treatment for HER2-positive mBC. The addition of trastuzumab to 100 mg/m<sup>2</sup> docetaxel for at least six cycles resulted in superior clinical efficacy with improved overall response rates (ORR), time to progressive disease, time to treatment failure, and duration of response (Marty et al. 2005).

Trastuzumab is well tolerated both as a single agent and in combination with standard chemotherapy (Cobleigh et al. 1998; Slamon et al. 2001). The most significant adverse event (AE) observed in patients who received trastuzumab was cardiac dysfunction, reflected by asymptomatic decreases in LVEF and, less frequently, by clinically symptomatic congestive heart failure (CHF). Risk factors for cardiac failure in the setting of trastuzumab treatment include co-administration with anthracycline-based chemotherapy, increasing age, declining LVEF during treatment to below the lower limit of normal, and the use of anti-hypertensive medications (Tan-Chiu et al. 2005).

Currently, the marketed formulation of trastuzumab is for intravenous administration (trastuzumab IV, Herceptin®). All available clinical data have been obtained with trastuzumab IV.

#### 1.2.2.1 Trastuzumab IV

The efficacy and safety of trastuzumab IV have been well characterized. Trastuzumab IV is administered to EBC patients for a total duration of one year. Adjuvant trastuzumab IV may be given as monotherapy, starting after completion of adjuvant chemotherapy, or in combination with the taxane component of adjuvant chemotherapy (followed by trastuzumab monotherapy). At the time of writing, adjuvant trastuzumab IV monotherapy is widely approved, and concurrent administration in combination with adjuvant chemotherapy is also approved or expected to be approved in many countries. Trastuzumab IV may be given weekly (q1w) or 3-weekly (q3w) to patients with mBC but in the adjuvant setting, when given as monotherapy, it is generally given q3w.

For the regulatory status and approved indications in specific countries, please refer to the current Herceptin (Ro 45-2317, Trastuzumab) Investigator's Brochure (IB) and local prescribing information.

#### 1.2.2.2 Pharmacokinetics of Trastuzumab IV

Based on a population pharmacokinetic (PK) analysis of data primarily from the mBC setting (Herceptin Report No. 1018264) the predicted median AUC (over a period of 3 weeks at steady-state) for the q1w and q3w regimens were 1677 and 1793 mg\*day/L, respectively, and the corresponding median C<sub>min</sub> values were 64.9 and 47.3 mg/L, respectively. A two-compartment model satisfactorily described the data. The typical trastuzumab IV PK parameters were as follows: clearance (CL) of 0.026 L/day and a volume of distribution of the central compartment (V<sub>c</sub>) of 3.17 L (which corresponds to human plasma volume, which is the V<sub>c</sub> characteristic of IgG immunoglobulins). The equilibrium half-life is about 26 days which is similar to that of endogenous IgG1 immunoglobulin (23 days) which constitutes the backbone of trastuzumab IV.

Refer to the Herceptin (Ro 45-2317, Trastuzumab) IB for further details regarding the pharmacokinetics of trastuzumab IV.

#### 1.2.2.3 Efficacy of Trastuzumab IV In Early Breast Cancer (Adjuvant Setting)

Six phase III multi-centre randomized controlled trials investigated the efficacy and safety of adjuvant trastuzumab IV in combination with or after standard adjuvant chemotherapy in the treatment of early breast cancer:

- Herceptin Adjuvant (HERA, BO16348) trial (Piccart-Gebhart et al. 2005; Smith et al. 2007; Gianni et al. 2011)
- North Central Cancer Treatment Group trial (NCCTG) N9831 trial (Romond et al. 2005; Perez et al. 2007; Perez et al. 2009; Perez et al. 2011)

- National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-31 (Romond et al. 2005; Perez et al. 2007; Perez et al. 2009; Perez et al. 2011)
- Breast Cancer International Research Group (BCIRG-006) study (Slamon et al. 2009, Slamon et al. 2011)
- Protocol Adjuvant dans le Cancer du Sein (PACS04) trial (Spielmann et al. 2009)
- Finland Herceptin (FinHer) trial (Joensuu et al. 2009).

Together, these trials accrued more than 15,000 women with node-positive or high-risk node-negative BC and used a variety of cytotoxic agents in various combinations, doses, and orders of administration. Four of these trials (HERA, N9831, B31 and BCIRG-006) are considered pivotal.

In the HERA study, trastuzumab treatment was started following completion of an approved neoadjuvant or adjuvant chemotherapeutic regimen (and radiotherapy as indicated) and continued for one or two years. In studies B31, N9831 and BCIRG-006, trastuzumab started after completion of four cycles of doxorubicin/cyclophosphamide and was administered for one year, either concurrently with four cycles of taxane chemotherapy (B31, N9831), or concurrently with six cycles of a non-anthracycline-containing taxane-based regimen (BCIRG-006), or after completion of chemotherapy.

All four pivotal randomized controlled trials (HERA, N9831, B31 and BCIRG-006) demonstrated significantly improved DFS, and three (HERA, B31 and BCIRG-006) demonstrated significantly improved OS. The DFS benefits were observed regardless of age, nodal status, hormonal status, or tumour size in all trials (Gianni et al. 2011; Slamon et al. 2011; Perez et al. 2011). Importantly, the most recent follow-up data from the HERA trial (Gianni et al. 2011) and the combined analysis of the NCCTG N9831 and NSABP B-31 trials (Perez et al. 2011) both demonstrate consistent DFS and OS advantages of adjuvant trastuzumab over a median follow-up of 4 years. Further, the significant benefits in DFS and OS were maintained over a median follow-up of approximately 5 ½ years in the BCIRG-006 study (Slamon et al. 2011), which is the longest follow-up reported to date. The long-term clinical benefits of one-year trastuzumab treatment clearly continue to outweigh the risks of adverse effects (Perez et al. 2011) and the regimen is considered standard of care with support from all major treatment guidelines (NCCN 2012; Gnant et al. 2011; Aebi et al. 2011).

Of the four pivotal randomized trials, the N9831 study was the only one to directly compare the concurrent and sequential use of trastuzumab. This study identified a strong trend for a 25% reduction in the risk of an outcome event when trastuzumab is started concurrently as compared to sequentially after paclitaxel (Perez et al. 2009). Therefore, based on a positive risk/benefit ratio, the authors recommended that trastuzumab be incorporated in a concurrent fashion when administered with paclitaxel (Perez et al. 2009), which also

resulted in the approval of the concurrent use of trastuzumab and chemotherapy.

For further details, refer to the current Herceptin (Ro 45-2317, Trastuzumab) IB.

#### 1.2.2.4 Efficacy of Trastuzumab IV in Early and Locally Advanced Breast Cancer (Neoadjuvant Setting)

Neoadjuvant chemotherapy is a defined treatment strategy for breast cancer, even though clinical trials in unselected patient populations have shown no difference in long term results between neoadjuvant and adjuvant chemotherapy. In these trials the effects of neoadjuvant chemotherapy were reported in terms of pathological complete response (pCR), or complete loco-regional eradication of invasive disease at the pathological post-surgical evaluation. This condition is considered as an indicator of the response to systemic treatment of micrometastases and it is regarded as a surrogate marker of better long-term survival.

Starting from the pivotal MDACC trial (Buzdar et al, 2007), the addition of trastuzumab to conventional neoadjuvant chemotherapy regimens for patients, homogeneously selected for the presence of HER2-positive disease, resulted in higher pCR in comparison with the control arm of chemotherapy alone. The likelihood of pCR in this studies varied from 31.7 to 66.7 %, with a few heterogeneity among the adopted evaluation criteria.

One of the most important studies is NOAH trial, where 228 HER-2-positive BC patients were randomly assigned to receive a neoadjuvant chemotherapy regimen consisting of doxorubicin, paclitaxel, cyclophosphamide, methotrexate and fluorouracil with or without trastuzumab given concurrently. Patients further received adjuvant trastuzumab for a total of 1 year. A parallel cohort of 99 patients with HER-2-negative disease was included and treated with the same chemotherapy regimen. In HER2-positive subset, pCR (ypT0-is ypN0) was significantly increased in the combination arm, 38%, in comparison with the chemotherapy alone arm, 20%. In addition to the advantage in the likelihood of pCR, the population of trastuzumab-treated patients showed a substantial improvement of event-free survival at 3 years, with a hazard ratio of 0.59 (95% CI: 0.38–0.90). Only two patients (2%) developed symptomatic cardiac failure that responded to treatment, and no cardiac deaths were reported (Gianni L et al, 2008).

The German GeparQuattro study also evaluated neoadjuvant trastuzumab. This randomized phase 3 trial assessed the incorporation of capecitabine in an anthracycline/taxane-based regimen and the concurrent use of trastuzumab with these chemotherapy regimens in HER-2-overexpressing patients. Of 1509 patients included, 445 patients had HER-2-positive BC and received trastuzumab (6 mg/kg) every 3 weeks concomitant with all chemotherapy cycles. pCR rate was higher in HER-2-positive disease compared with the HER-2-negative group (31.7% versus 15.7%). In the subgroup of patients that did not respond to epirubicin/cyclophosphamide, the pCR rate was also higher

in HER-2-positive versus HER-2-negative tumours (16.7% versus 3.3%). Grade 3 and 4 neutropenia as well as conjunctivitis were seen in the trastuzumab-treated group, but there were no cardiac safety concerns (von Minckwitz et al, 2010).

These trials prompted to the conventional incorporation of trastuzumab into the neoadjuvant regimens for women with HER2-positive disease.

#### 1.2.2.5 Safety of Trastuzumab IV

##### 1.2.2.5.1 Cardiac Safety of Trastuzumab IV

The most clinically relevant AE associated with trastuzumab IV is left ventricular cardiac dysfunction (e.g. CHF). In patients with HER2-positive EBC enrolled in pivotal clinical trials described in Section 1.2.2.3, trastuzumab treatment for 1 year (administered concurrently or sequentially with chemotherapy) appeared to be associated with a decrease in LVEF, an increase in the incidence of CHF (where specified, this was severe [New York Heart Association or NYHA] class III or IV or grade 3 or 4 or symptomatic CHF) and discontinuation of treatment as a result of cardiac AEs (Garnock-Jones et al. 2010). Cardiac toxicity described as NYHA class III/IV CHF occurred in 0%–0.9% of patients in the control arms and in 0%–3.8% of patients in the trastuzumab-containing arms of the four pivotal trials (HERA, N9831, B31 and BCIRG-006). However, the cardiotoxicity observed with concurrent or sequential trastuzumab treatment appeared to be mostly reversible following trastuzumab discontinuation, and no significant increase in cardiac death was reported (Garnock-Jones et al. 2010).

An overview of cardiac safety data from selected trials of trastuzumab in combination with a taxane after anthracyclines for HER2-overexpressing EBC shows rates of symptomatic or severe CHF of < 4% and asymptomatic declines in left ventricular ejection fractions of > 10 points in ≤ 30% of patients. However, inter-study comparisons of chemotherapy-induced cardiac dysfunction are difficult because of the use of different definitions of cardiac dysfunction and different parameters for assessing cardiac safety (Ewer and O'Shaughnessy 2007). These levels were considered below safety cut-off points set by the individual studies' independent data monitoring committees (Jahanzeb et al. 2008).

The NSABP B-31 trial determined the 5-year cumulative cardiac event rate (NYHA class III or IV CHF or cardiac death) to be 3.8% in patients randomly assigned to trastuzumab versus 0.9% in patients who received chemotherapy alone (Rastogi et al. 2007, Russell et al. 2010). In the NCCTG N9831 trial, the incidence of CHF was 0% in the chemotherapy-alone arm, 2.2% in patients who received sequential chemotherapy and trastuzumab, and 3.3% in patients who received concurrent chemotherapy and trastuzumab (Perez et al. 2008). An independent adjudication of the cardiac events occurring in studies B-31 and N9831 determined that the incidence of symptomatic heart failure events



was 2.0% in trastuzumab-treated patients compared with 0.45% in the chemotherapy-alone arm, and that the majority (86%) of these patients recovered with appropriate treatment (Russell et al. 2010).

The long-term incidence of cardiac AEs in patients with eBC who were treated with trastuzumab IV for 1 year after completion of neoadjuvant or adjuvant chemotherapy was also evaluated in the HERA trial. Of the 1,698 patients randomly assigned to observation and 1,703 randomly assigned to 1 year of trastuzumab treatment, 94% had been treated with anthracyclines. The incidence of discontinuation of trastuzumab because of cardiac disorders was low (5.1%). At a median follow-up of 3.6 years, the incidence of cardiac end points remained low, though it was higher in the trastuzumab group than in the observation group (severe CHF, 0.8% vs. 0.0%, respectively; confirmed significant LVEF decreases, 3.6% vs. 0.6%, respectively). In the trastuzumab group, 59 of 73 patients with a cardiac end point reached acute recovery (Procter et al. 2010).

#### 1.2.2.5.2 Post-Marketing Safety Summary of Trastuzumab IV

It is estimated that over one million patients have been treated with trastuzumab IV as of October 2011 (Roche, Data on file).

The most common (occurring in  $\geq 1$  out of 10 treated patients) adverse reactions are infusion-associated symptoms such as fever and chills, usually following the first infusion of trastuzumab IV. These symptoms are usually mild to moderate in severity and occur infrequently with subsequent trastuzumab IV infusions in up to 40% of patients. Other very common ( $\geq 1/10$  patients) adverse reactions include febrile neutropenia, tremor, dizziness, headache, blood pressure changes (increase or decrease), irregular heartbeat, palpitation, cardiac flutter, decreased ejection fraction, dyspnea, wheezing, diarrhea, vomiting, nausea, lip swelling, abdominal pain, erythema, rash, swelling of the face, arthralgia, muscle tightness, myalgia, asthenia, chest pain, fatigue, influenza-like symptoms, infusion-related reaction, and pain.

Some adverse reactions to trastuzumab IV infusion can be serious and include dyspnea, hypotension, elevated blood pressure, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, and respiratory distress. In the post-marketing setting, very rare ( $< 1/10,000$ ) occurrences of severe infusion reactions leading to a fatal outcome have been associated with the use of trastuzumab IV.

Severe pulmonary events leading to death have been reported with the use of trastuzumab IV in the post-marketing setting (4 out of 10,000 treated patients). Signs, symptoms, and clinical findings included interstitial lung disease including pulmonary infiltrates, acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary edema, and pulmonary insufficiency. These events may or may not occur as sequelae of infusion reactions. Patients with symptomatic intrinsic lung disease or with extensive tumour involvement of the lungs, resulting in dyspnea at rest, may be

at greater risk of severe reactions. Other risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies such as taxanes, gemcitabine, vinorelbine and radiation therapy.

In addition, severe hypersensitivity reactions have been infrequently reported in patients treated with trastuzumab IV (the exact incidence of these events is unknown). Signs and symptoms include anaphylaxis, urticaria, bronchospasm, angioedema, and/or hypotension. In some cases, the reactions have been fatal. Symptom onset generally occurred during an infusion, but onset after the completion of an infusion has also been reported. Reactions were most commonly reported in association with the initial infusion.

The immunogenicity of trastuzumab IV has been investigated in clinical studies that included 903 MBC patients. Human anti-human antibodies to trastuzumab were detected in one patient, who had no allergic manifestations.

More detailed information on the full safety profile of trastuzumab IV is found in the Herceptin (Ro 45-2317, Trastuzumab) IB.

#### 1.2.2.6 Trastuzumab SC

Trastuzumab for subcutaneous (SC) administration has been developed by F. Hoffmann-La Roche Ltd to address the known limitations of IV administration (e.g. infusion-related reactions, long administration times, requirement for hospital facilities, treatment barrier for patients with poor venous access, continued use of port-a-cath systems). Administration of trastuzumab SC takes significantly less time (up to 5 minutes) compared to IV infusion (30 to 90 minutes) and this is expected to improve treatment convenience and compliance. These attributes are particularly important for patients treated over prolonged periods of time. In clinical studies conducted to date, administration of trastuzumab SC is associated with a reduced frequency and intensity of administration-related reactions. Such reduction in adverse effects of administration has also been observed with another monoclonal antibody, alemtuzumab (MabCampath<sup>®</sup>) (Lundin et al. 2002). Treatment fatigue has been reported to lead to premature treatment cessation in a small proportion of patients treated with chemotherapy (Coates et al. 1983).

In the HannahH study (a Phase III randomized, open-label, international study of the SC formulation of trastuzumab in HER2-positive eBC patients), the safety profile of trastuzumab SC was comparable to that of trastuzumab IV (Jackisch et al. 2012). Subcutaneous injection of trastuzumab SC formulation was generally well tolerated with a low incidence of injection site reactions (grades 1 and 2). These findings support the potential of trastuzumab SC to provide improved convenience for patients compared to the existing IV formulation (Pivot et al. 2012). In addition, SC administration also offers the potential for administration of trastuzumab outside a hospital/outpatient clinic setting in the future, further improving convenience and compliance.

The feasibility and patient acceptability of subcutaneous administration of any drug is dependent on the volume that must be administered. A key excipient in

the subcutaneous formulation is the enzyme hyaluronidase, which enables larger volumes to be administered without a decrease in patient acceptability. Animal-derived hyaluronidase has been available commercially for over 60 years and is used primarily as a permeation enhancer to increase the dispersion and absorption of other co-administered drugs. Hyaluronidase transiently hydrolyses hyaluronan, a matrix component of the subcutaneous matrix. The hydrolysis leads to decreased viscosity of the subcutaneous matrix and, thus, to an improved delivery of subcutaneous administered drugs to the systemic circulation. The decreased viscosity is also expected to facilitate subcutaneous administration of larger volumes of fluid.

For information on the subcutaneous formulation please refer to the BP22023, CP2 (Section 1.2.2.6.2.2.1) and BO22227, HannaH studies (Section 1.2.2.6.2.3).

More recently, preparations of recombinant humanized hyaluronidase (rHuPH20) have become available. rHuPH20 has a higher purity and is associated with improved efficacy and tolerability compared with the animal-derived enzyme. In the United States, one recombinant humanized hyaluronidase (Hylenex® [Hylenex: Full Prescribing Information]) is licensed to facilitate the absorption and dispersion of drugs when given subcutaneous at doses between 50 IU and 300 IU (Frost et al. 2007). The rHuPH20 used in this study is generated from a second generation of the Hylenex® process (Gen 2 process) with an improved yield and purity.

#### 1.2.2.6.1 RECOMBINANT HUMAN HYALURONIDASE (rHuPH20)

##### 1.2.2.6.1.1 NON CLINICAL STUDIES WITH rHuPH20

After IV administration in the dose range 0.3 to 30 mg/kg, rHuPH20 demonstrated nonlinear PK, rapid clearance and a half-life of around 5 minutes at the lowest dose tested. The bioavailability of rHuPH20 following subcutaneous administration was extremely low (not determinable at low doses, 6% to 8% in the dose range 3 to 30 mg/kg). Treatment of various species with rHuPH20 (IV or SC) was generally well tolerated and no major abnormalities were noted in any toxicology studies.

For details on non-clinical studies with rHuPH20 please refer to the Herceptin® Investigator's Brochure.

##### 1.2.2.6.1.2 Clinical Studies with rHuPH20

The safety and efficacy of hyaluronidase products have been widely established. The most significant safety risk identified is hypersensitivity/allergenicity, which is thought to be related to the lack of purity of the animal-derived preparations (Frost et al. 2007, Harris 2003). The purity and hence the safety risks of hyaluronidase preparations have further been enhanced by the development of the humanized recombinant enzyme rHuPH20. Clinical data are available from four studies with rHuPH20.

- In an allergic sensitivity study (R04-0851), 100 healthy volunteers were injected intradermally with 0.1 mL (15 U) of rHuPH20 and saline control. The most common side effects were generally mild redness, bruising, swelling, discomfort and itching. No AEs were serious and none were judged to be related to study treatment
- A proof-of-concept dose escalation study (HZ2-06-02) with adalimumab and rHuPH20 in 15 patients with rheumatoid arthritis evaluated the effects of rHuPH20 on the PK, safety and tolerability of adalimumab. A single co-administration of adalimumab with rHuPH20 increased adalimumab exposure by a weighted average of 13% compared to adalimumab alone. The injection was well tolerated with only mild and moderate AEs
- HZ2-07-01 was a double-blinded, within-subject-controlled, two way cross-over study comparing the time to inject (flow rate), safety and tolerability of a subcutaneous administered 10% (2,000 mg in 20 mL) solution of immunoglobulin G (diluted Carimune® NF) with and without rHuPH20 in 30 healthy volunteers. There was a statistically non-significant trend towards a decrease in time to inject and an increase in flow rate in the presence of rHuPH20 relative to the control group. The most common AEs were injection site reactions, consisting of erythema, pain, edema, induration or pruritus (communication Halozyme Therapeutics Inc. on preliminary study results)
- HZ2-07-02 investigated the subcutaneous injection of different rHuPH20 concentrations in a viscous solution of IgG and adalimumab in healthy volunteers using different volumes of injection (2, 8 and 16 mL). The maximum total enzyme dose administered in this study was 96,000 U. The injections were well tolerated with no serious adverse events (SAEs) reported. All injection site reactions such as erythema, pain and induration were mild (98%) or moderate (2%) in severity. There was a trend to lower mean time to inject in subjects who received rHuPH20 compared to those who received injections without rHuPH20, as well as a trend towards an increase in the exposure to adalimumab in the presence of rHuPH20. Pain increased across all volume cohorts after injection, with no clear difference between the presence and absence of rHuPH20. The highest total rHuPH20 dose administered in the clinical studies was 96,000 U and this was well tolerated by healthy volunteers.

Overall, the results of these studies have shown that rHuPH20 is generally well tolerated, with no SAEs reported. AEs were mild or moderate in severity and most were injection site reactions. The highest total rHuPH20 dose administered in the clinical studies was 96,000 U and this was well tolerated by healthy volunteers.

For detailed information on the clinical trials conducted with rHuPH20, please refer to the Herceptin® Investigator's Brochure.

#### 1.2.2.7 Non Clinical Studies with Trastuzumab SC

An overview of completed non-clinical pharmacology, PK, and toxicology studies for trastuzumab subcutaneous is provided in the Herceptin® Investigator's Brochure. Overall, these studies showed that rHuPH20 enabled more rapid absorption of trastuzumab SC, and that subcutaneous administration of trastuzumab formulated with rHuPH20 was well tolerated locally and systemically.

#### 1.2.2.8 Clinical Studies With Trastuzumab SC

Trastuzumab SC (formulated with rHuPH20) has been reported in two completed clinical trials (BP22023, CP2 and BO22227, HannaH) (Wynne et al. 2010; Ismael et al, 2012) using conventional syringe and hypodermic needle for administration. In addition, the recently completed study (BO25532, CP3) demonstrated comparable exposure between subcutaneous administration with the single-use injection device (SID) versus with the conventional syringe and needle (Wynne et al. 2012). A patient preference and health care professional (HCP) satisfaction study (MO22982, PrefHer) comparing trastuzumab subcutaneous administration using SID or hand-held syringe with conventional administration of trastuzumab IV administration is currently ongoing. A Phase III prospective study (MO28048, SafeHer) to assess the safety of trastuzumab SC (manual administration via hand-held syringe or SID) as adjuvant therapy in patients with operable HER2-positive EBC has been recently initiated.

An overview of the clinical development of Trastuzumab SC is presented in Table 1. As shown a pharmacokinetics study is completed and several phase II and III studies are ongoing.

**Table 1 Overview of the Clinical Development Program of SC Trastuzumab**

Studies	Status	Design	Primary Objective
<b>Trastuzumab SC (vial)</b>			
Phase Ib Dose-finding Study (BP22023, CP2)	Completed	Dose-finding/dose confirmation study OL, PG, single dose, MC	Select the dose of trastuzumab SC which results in comparable exposure to that achieved from an IV dose of trastuzumab
Phase III Clinical Study (BO22227, Hannah)	Completed	PK, efficacy and safety study in the neoadjuvant/adjuvant setting OL, PG, randomized, multiple-dose, MC	Non-inferiority of pre-surgery trastuzumab C <sub>trough</sub> and pCR
Phase I Device Qualification Study (BO25532, CP3)	Completed	PK bridging to injection device OL, PG, randomized, single dose, MC	PK comparability of trastuzumab SC dosing via a SID or via hand-held needle and syringe used in previous clinical studies.
<b>Additional Studies</b>			
Phase II Patient Preference Study (MO22982, PrefHER)	Ongoing	Patient preference and HCP satisfaction study Randomized, MC, cross-over study and PK study	To evaluate patient preference for trastuzumab SC administration using a SID/ hand-held needle and syringe or trastuzumab IV
Phase III Safety Study [MO28048, SafeHer]	Ongoing	Safety Study Non-randomized two-cohort, MC, OL	To evaluate the safety of assisted- and self-administered trastuzumab SC as adjuvant therapy
HCP: Health Care Professional; MC: Multi-centre; OL: Open-label; pCR: pathological complete response; PG: Parallel group; PK: pharmacokinetic; SID: single use injection device			

See the Herceptin Investigator's Brochure for details on clinical studies.

#### 1.2.2.8.1 Study BP22023

Study BP22023 (CP2, Wynne et al. 2010) was a dose-finding study of trastuzumab SC, conducted in healthy male volunteers and patients with HER2-positive EBC. Part 1 of the study was designed to select a trastuzumab SC dose (formulated with rHuPH20) that resulted in comparable exposure and trough levels at least as high as those achieved with trastuzumab IV at dose of 6 mg/kg. Part 2 of the study was designed to confirm the subcutaneous dose selected from part 1. Twenty-four healthy male subjects and 42 female patients with HER2-positive eBC received single doses of either IV or trastuzumab SC.

In Part 1, a total of 86 AEs were observed in 27 subjects/patients. Of these, 71% were considered to be mild, 28% moderate and there was one SAE (an infusion-related reaction [IRR]).

In Cohort 1, in which male healthy volunteers received trastuzumab IV at 6 mg/kg, the most commonly observed AEs were headache (3 AEs), musculoskeletal pain (2), diarrhea (2), abdominal pain (2) and IRR (2).

In Cohort 2, in which female patients received trastuzumab IV at 6 mg/kg, the most commonly observed AE was headache which occurred in 2 patients.

In Cohorts 3 to 5, in which male subjects received trastuzumab SC at 6, 8 and 10 mg/kg, there was no apparent dose-related increase in AEs and subcutaneous administration was generally well tolerated. The most commonly observed AEs were headache (4 events; 3 mild, 1 moderate), upper respiratory tract infection (4 events; all mild) and influenza-like illness (3 events; 2 moderate, 1 mild).

In Part 2, a total of 181 AEs were observed in 39 female patients. Of these, 72.5% were considered to be mild, 25.5% moderate and there were four (2%) severe AEs.

In Cohorts A and B, there was no apparent dose-related increase in AEs and subcutaneous administration was generally well tolerated. The most commonly observed AEs in these patients were headache (27 events; 18 mild, 8 moderate, 1 severe), diarrhea (8 events; 6 mild, 2 moderate), lethargy (6 events; 4 mild, 2 moderate) and injection site erythema (6 events; all mild).

As this was the first study during which subjects/patients received trastuzumab SC, special consideration was given to the local tolerability related to drug administration. In subjects/patients who received trastuzumab SC, there were 18 AEs that were classified as administration site conditions. All but two of these AEs were mild in severity. There were two instances of moderate injection site pain.

No deaths or serious AEs (SAEs) occurred in this study.

#### 1.2.2.8.2 Study BO22227

Study BO22227 (HannaH) compared the PK profile, efficacy, and safety of the subcutaneous and IV formulations in patients with HER2-positive eBC. The HannaH study was a phase III, randomized, international, open-label, trial in the (neo)adjuvant setting.

Patients with HER2-positive, operable, locally advanced or inflammatory BC were randomly assigned to eight cycles of neoadjuvant chemotherapy administered concurrently with trastuzumab every 3 weeks either IV (8 mg/kg loading dose, 6 mg/kg maintenance dose) or subcutaneous (fixed dose of 600 mg); 1:1 ratio. Chemotherapy consisted of four cycles of docetaxel (75 mg/m<sup>2</sup>) followed by four cycles of fluorouracil (500 mg/m<sup>2</sup>), epirubicin (75 mg/m<sup>2</sup>), and cyclophosphamide (500 mg/m<sup>2</sup>), every 3 weeks. After surgery, patients continued trastuzumab to complete 1 year of treatment. Co-primary endpoints were serum trough concentration (C<sub>trough</sub>) at predose cycle 8 before surgery (non-inferiority margin for the ratio between groups of 0.80) and pathological complete response (pCR; non-inferiority margin for the difference between groups of -12.5%), analyzed in the per-protocol population. This study is registered with ClinicalTrials.gov, number NCT00950300. Finding: 299 patients were randomly assigned to receive intravenous trastuzumab and 297 to receive trastuzumab SC. The geometric mean pre-surgery C<sub>trough</sub> was 51.8 µg/mL (coefficient of variation 52.5%) in the IV group and 69.0 µg/mL (55.8%) in the subcutaneous group. The geometric mean ratio of C<sub>trough</sub> subcutaneous to C<sub>trough</sub> IV was 1.33 (90% CI 1.24–1.44). 107 (40.7%) of 263 patients in the IV group and 118 (45.4%) of 260 in the subcutaneous group achieved a pCR. The difference between groups in pCR was 4.7% (95% CI -4.0 to 13.4). Thus trastuzumab SC was non-inferior to trastuzumab IV for both co-primary endpoints. The incidence of grade 3–5 adverse events was similar between groups. The most common of these adverse events were neutropenia (99 [33.2%] of 298 patients in the IV group vs 86 [29.0%] of 297 in the subcutaneous group), leucopenia (17 [5.7%] vs 12 [4.0%]), and febrile neutropenia (10 [3.4%] vs 17 [5.7%]). However, more patients had SAE in the subcutaneous group (62 [21%] of 297 patients) than in the IV group (37 [12%] of 298); the difference was mainly attributable to infections and infestations (24 [8.1%] in the subcutaneous group vs 13 [4.4%] in the IV group). Four AEs led to death (one in the intravenous group and three in the subcutaneous group), all of which occurred during the neoadjuvant phase. Of these, two—both in the subcutaneous group—were deemed to be treatment related. Trastuzumab SC, administered over about 5 min, has a PK profile and efficacy non-inferior to standard IV administration, with a similar safety profile to trastuzumab IV, and therefore offers a valid treatment alternative. No new safety signals were identified with trastuzumab SC (Ismael et al. 2012).

#### 1.2.2.8.3 Study BO25532

Study BO25532 (CP3) was a randomized, open-label, parallel, 2-arm, multi-centre Phase I study to investigate the comparability of PK of trastuzumab



administered subcutaneously using either the SID or a conventional syringe and hypodermic needle. The study also assessed the performance of the SID and evaluated the immunogenicity of trastuzumab and rHuPH20.

Enrolment was completed in September 2011, with a total of 119 healthy male subjects randomized 1:1 to receive a single 600 mg subcutaneous injection by either administration method. The primary objective of the study was met, with the results for both co-primary PK endpoints within the standard bioequivalence range of [0.8, 1.25], meeting the pre-specified criteria for comparability. Sensitivity analyses of the co-primary endpoints that included non-dose normalized or non-body-weight adjusted calculations were in line with the primary analysis.

Trastuzumab was well tolerated after single-dose administration by both methods and no apparent differences related to the injection method were observed (Wynne et al. 2012).

#### 1.2.2.8.4 Ongoing Studies

##### **STUDY MO22982**

MO22982 (PrefHer) is a Phase II international, randomized, open-label, two-cohort, two-arm crossover study to evaluate patient's preference and HCP satisfaction with subcutaneous versus IV administration of trastuzumab in HER2-positive EBC, following surgery and completion of chemotherapy (neoadjuvant or adjuvant). As (neo)adjuvant treatment may also include trastuzumab, randomized patients are stratified by de novo vs. non de novo trastuzumab. Patients in Arm A receive trastuzumab SC (4 cycles) followed by trastuzumab IV (4 cycles). Patients randomized to Arm B receive trastuzumab IV (4 cycles) followed by trastuzumab SC (4 cycles). Patients enrolled into Cohort 1 receive trastuzumab SC administered via a SID, and patients enrolled into Cohort 2 receive trastuzumab SC administered from a vial with a hand-held syringe. An estimated 200 patients will be randomized to obtain at least 160 evaluable patients in each cohort, giving a total of approximately 400 patients to obtain 320 evaluable patients. The enrollment of Cohort 1 patients is complete, enrollment of Cohort 2 patients is ongoing.

##### **STUDY MO28048**

MO28048 (SafeHer) is a Phase III, prospective, two-cohort, non-randomized, multicenter, multinational, open label study to assess the safety of assisted- and self-administered trastuzumab SC as adjuvant therapy in patients with operable HER2-positive eBC. Approximately 2,500 patients with HER2-positive eBC whose tumor has been excised will be enrolled into the study. The trial is ongoing and will be conducted at approximately 500 centers in approximately 60 countries.

#### 1.2.2.9 Subcutaneous Single-Use Injection Device (SID)

The SID is a single-use device for the subcutaneous administration/injection of medicinal products such as trastuzumab. The medicinal product to be injected

is contained in an integral non-removable cartridge and the entire content of the cartridge is delivered to the patient in a single injection through a needle that retracts when the injection is complete. The administration rate is fixed (approximately 1.5 mL/min) and the dosage delivered is pre-set and controlled at the product manufacturing stage. The device deploys a mechanism to retract the needle when the injection is completed, preventing handling injuries. The trastuzumab SID will administer trastuzumab (600 mg) (formulated with 10,000U of rHuPH20). The device will be applied to the patient's thigh and activated by study staff. Information on the preparation for use of the SID is provided in a separate leaflet.

Trastuzumab SC (SID) is supplied in a SID. The cartridge included in the SID contains a nominal content 120 mg/mL of trastuzumab mixed with 2,000 U/mL rHuPH20) in 5mL. Information on the preparation for use of the SID is provided in a separate leaflet.

Trastuzumab SC for manual injection will be supplied in a vial containing a ready to use solution with a nominal content of 120 mg/mL of trastuzumab mixed with 2,000 U/mL rHuPH20 in 5mL and must not be diluted prior to administration. The solution is injected using a hand-held syringe fitted with a 27 gauge needle. Further information on the preparation and administration is provided as a separate leaflet.

### 1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Trastuzumab SC is a new administration route that has demonstrated similar PK and efficacy in pCR in the treatment of HER2-positive eBC in the neoadjuvant setting, during which no new safety signals were identified.

This study is a Phase IIIb, open-label, multicenter study to assess the safety and tolerability of trastuzumab solution injected subcutaneously (vial or SID) in patients with HER2-positive eBC. In addition efficacy parameters (disease free survival and overall survival), exposure to study medication, duration of treatment, follow-up and safety follow-up will be analysed. This study is a part (Daughter study) of global umbrella study. Safety and efficacy data will be collected in local (Daughter) study and transferred to a global database for a pooled analysis. This study will be run in order to gain a better understanding of the safety profil of trastuzumab SC.

#### 1.3.1 RATIONALE FOR TEST PRODUCT DOSAGE

##### 1.3.1.1 Trastuzumab SC

Trastuzumab SC will be given q3w at a fixed dose of 600 mg. Use of a fixed dose for all patients and all cycles greatly simplifies dosing, reduces the potential for error, and reduces wastage. Fixed doses have been used for other therapeutic monoclonal antibodies, particularly in chronic conditions, such as rheumatoid arthritis (e.g. adalimumab). The fixed dose of trastuzumab for subcutaneous administration was selected with the aim of achieving

trastuzumab serum trough concentrations (C<sub>trough</sub>) that are non-inferior to those obtained with q3w trastuzumab IV administration. The fixed (600 mg) dose of trastuzumab used in this study was calculated based on PK modelling of preliminary data from the BP22023 study (see section 1.2.2.8.1) which showed that 600 mg doses of trastuzumab SC were able to achieve serum C<sub>trough</sub> levels at least as high as those achieved with standard weight-adjusted trastuzumab IV dosing. Trastuzumab exhibits linear pharmacokinetics in the clinical dose range, which is an indication that target receptors are saturated. Therefore, achieving C<sub>trough</sub> levels with subcutaneous administration that are at least as high as with the IV dosing, indicates that efficacy should be comparable. Patients with lower body weight may be exposed to higher C<sub>trough</sub> levels than if they were dosed on a weight-adjusted basis. However, studies in which higher than standard (or more frequent) doses of trastuzumab were given (Clinical Study Report 1026709; Vogel et al. 2002) and reports of patients accidentally overdosed with trastuzumab IV, do not indicate any detrimental effect on patient safety. Moreover, based on data from the BP22023 study, the predicted maximal concentrations following eight q3w cycles of 600 mg are expected to be below the C<sub>trough</sub> of trastuzumab IV observed in the MO16982 study (range 199-375 mg/L). In study MO16982 patients were initially dosed with 6 mg/kg weekly and no increase in AEs was observed (Clinical Study Report 1026709). More recently, results of the HannaH study (BO22227) have been released. The study met its two co-primary endpoints, i.e. observed trastuzumab C<sub>trough</sub> after 7 cycles and the primary efficacy variable of pathological complete response, thereby demonstrating comparable bioavailability and efficacy of the subcutaneous and IV formulations of trastuzumab. The fixed dose of 600 mg of trastuzumab SC will be administered with a fixed dose of 10,000 U of rHuPH20 (2,000 U/ml). The dose of rHuPH20 was selected based on non-clinical PK studies with a number of antibodies, including trastuzumab. These studies showed a trend for increasing dispersion and absorption with increasing concentrations of rHuPH20 (Clinical Study Report 1029906; Halozyme Study Report). Of note, a higher amount of rHuPH20 (6,000 U/ml) did not improve the absorption of trastuzumab as compared to a formulation containing 2,000 U/ml rHuPH20. The selected rHuPH20 concentration was further verified in clinical studies for satisfactory absorption parameters. Non-clinical and clinical data demonstrate that the selected amount of rHuPH20 contained in the trastuzumab SC formulation is well-tolerated.

### 1.3.2 RATIONALE FOR PATIENTS

Surgery is the main modality of local treatment for BC (with or without radiotherapy) and can control loco-regional disease in the majority of patients. Systemic chemotherapy (or endocrine therapy in hormone receptor-positive patients) reduces the risk of relapse and is given either prior to surgery (neoadjuvant therapy) or following surgery (adjuvant therapy) or both. Cytotoxic chemotherapy, endocrine therapy, radiotherapy, and molecular targeted therapies currently represent the backbone of modern systemic BC treatment.

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Patients with HER2-positive eBC frequently require extensive treatment lasting months or years. Many require surgery, adjuvant chemotherapy (usually given IV for 4-6 months) and/or hormonal therapy, and radiotherapy (often given daily for 4-6 weeks), as well as trastuzumab. Adjuvant trastuzumab is given IV q1w or q3w for a total of one year. This necessitates regular clinic visits and, when started after completion of adjuvant chemotherapy and adjuvant radiotherapy if indicated, it greatly extends the period of time over which the patient is obliged to attend the hospital or clinic which can cause inconvenience and increased costs to patients. Even when started concurrently with the taxane component of chemotherapy (Herceptin license permitting), trastuzumab monotherapy still continues for several months after completion of other systemic therapy.

Trastuzumab infusions are given over 30 to 90 minutes (or longer if there are infusion-related symptoms). Subcutaneous administration of trastuzumab is quicker (lasting up to 5 minutes) and this alone could improve convenience for patients (and clinic staff).

Furthermore, subcutaneous administration does not require IV access (which can be problematic in some patients after completion of chemotherapy) and, based on the findings of the BP22023 study (Wynne et al. 2010) and previous observations with subcutaneous alemtuzumab administration (Lundin et al. 2002), may reduce the incidence of infusion-related symptoms. Use of a SID may also enable self-administration of trastuzumab in the future. This could potentially further improve convenience for patients and compliance with therapy.

The most clinically relevant AE associated with trastuzumab IV is left ventricular cardiac dysfunction or CHF. Cardiac toxicity, as measured by the rate of NYHA class III/IV CHF was the most significant AE, occurring in 0%–3.8% of patients in the trastuzumab-containing arms of six randomized adjuvant trials. The current study is designed to investigate the safety and tolerability of two subcutaneous administration methods for trastuzumab in the (Neo)-adjuvant setting, i.e. assisted administration using a conventional syringe (vial formulation) and self-administration using a SID. The observed LVEF rate served as basis for the determining the sample size for the current trial. Patient satisfaction with self-administration using a SID is assessed as part of the secondary objectives of the study.

Trastuzumab is now a standard component of adjuvant treatment in patients with HER2-positive eBC. The trastuzumab SC dose selected for this study is consistent with the findings of the BP22023 (CP2) trial and identical to that evaluated in the recently completed BO22227 (HannaH) study (see Section 1.2.2.8.1f or details). Efficacy is hence expected to be comparable to that observed in trastuzumab IV trials. Safety data from the BP22023 and BO22227 studies show that trastuzumab SC is well tolerated, with no safety signals detected compared to trastuzumab IV in the BO22227 study. The benefit to risk ratio of adjuvant trastuzumab SC in the current trial is therefore expected to be

favorable. Further, the convenience of subcutaneous administration of trastuzumab will give patients greater independence which is expected to increase compliance.

Several targeted drugs with different molecular pathways have achieved approval for mBC, but trastuzumab is the only such therapy that is currently approved for adjuvant or neoadjuvant treatment of eBC (Untch 2010). The use of trastuzumab in the adjuvant setting is also supported by international treatment guidelines for women with HER2-positive BC (NCCN 2012; Goldhirsch et al. 2011; Aebi et al. 2011). The introduction of trastuzumab at the end of 1990s has particularly improved the outcome for eBC patients with HER2-positive disease (Colozza et al. 2006).

### 1.3.3 BENEFITS OF SC ADMINISTRATION OF TRASTUZUMAB

The current marketed formulation of trastuzumab is for IV administration. Trastuzumab infusions are given over 30 to 90 minutes (or longer if there are infusion-related symptoms). The administration of trastuzumab necessitates regular clinic visits and when started after completion of adjuvant chemotherapy (and adjuvant radiotherapy, if indicated), greatly extends the period of time over which the patient is obliged to attend the hospital or clinic, at great inconvenience and cost. Even when started concurrently with the taxane component of chemotherapy (Herceptin® license permitting), trastuzumab monotherapy still continues for several months after completion of other systemic therapy. Subcutaneous administration of trastuzumab is quicker (lasting approximately 5 minutes) and this alone could improve convenience for patients (and clinic staff). Furthermore, subcutaneous administration does not require IV access, which can be problematic in some patients after completion of chemotherapy. Use of a pre-loaded SID should also reduce preparation time for pharmacy or clinic staff and might, in the future, enable administration outside a hospital/outpatient clinic setting. This SID could potentially further improve convenience for patients and compliance with therapy. The patient SID Satisfaction Questionnaire, developed for use in Study MO28048, will be used in the current study to collect data on patient satisfaction, comfort level and convenience of trastuzumab administrations using the SID. It is expected that with the switch from IV to subcutaneous administration route, HCP time would be saved. Time gained could be invested in other patient care activities, or increase the number of patients that could be treated at a site. Further it is expected that the amount of medical supplies and resources required would be reduced.

Trastuzumab SC (formulated with rHuPH20) has been evaluated in three completed clinical trial: BP22023 (CP2), BO22227 (HannaH) a clinical trial using conventional syringes and hypodermic needles for administration and a PK study BO25532 (CP3) to demonstrate comparable exposure between subcutaneous administration with the SID versus with the conventional syringe and needle. Trastuzumab was well tolerated after single-dose administration by

both methods and no apparent differences related to the injection method were observed (Wynne et al. 2012). Two clinical trial with trastuzumab SC are ongoing in patients with eBC: MO22982 (PrefHer) will evaluate patient's preference and HCP satisfaction, and MO28048 (SafeHer) will assess the safety of assisted- and self-administered trastuzumab SC (see Section 1.2.2.8.4)

As mentioned earlier, trastuzumab is now a standard component of adjuvant treatment in patients with HER2-positive eBC, and is supported by all major treatment guidelines. The long-term benefits trastuzumab IV treatments have been demonstrated. The dosing of trastuzumab SC in this study has been chosen to achieve serum trough levels at least as high as those achieved by the IV formulation.

Efficacy of trastuzumab SC is hence expected to be comparable to IV. Trastuzumab IV has an established safety profile, supported by a clinical database comprised of approximately 14,000 female patients with HER2-positive eBC (in addition to patients with HER2-positive MBC). Safety data from the BP22023 and BO22227 studies show that trastuzumab SC is well tolerated, with no new safety signals detected compared to trastuzumab IV in the BO22227 study. The benefit to risk ratio of trastuzumab SC administration in this trial is therefore expected to be favorable. The main advantage of trastuzumab SC is the reduced administration time (approximately 5 minutes) compared to the IV infusions. The convenience of subcutaneous administration of trastuzumab using a single-use pre filled device (SID) will give patients greater independence which is believed to increase compliance and to lead to an improved quality of life.

Beside improving patients convenience and comfort, subcutaneous administration of trastuzumab may also optimize medical resource utilization by reducing administration time, requiring no dedicated infusion staff and no need for infusion bag preparation.

## **2. OBJECTIVES**

### **2.1 PRIMARY OBJECTIVE**

The primary objective of the study is to assess the safety and tolerability of trastuzumab solution injected subcutaneously (vial or single-use injection device [SID]) in patients with HER2-positive early breast cancer (EBC) or locally advanced breast cancer (LABC).

### **2.2 SECONDARY OBJECTIVES**

The secondary objectives for this study are the following:

- Exposure to study medication
- Duration of treatment, follow-up, and safety observation

- Efficacy:
  - overall survival (OS), disease-free survival (DFS)
  - In the Neo-adjuvant setting activity of two sequential drug regimens, Anthracycline-containing regimen followed by concomitant administration of Taxane and Trastuzumab SC, assessed as the incidence of pathological Complete Response in breast and nodes (pCR; ypT0-is ypN0)
- Patient Satisfaction using SID (single use injection device)
- HCP satisfaction

### 2.3 EXPLORATORY OBJECTIVES

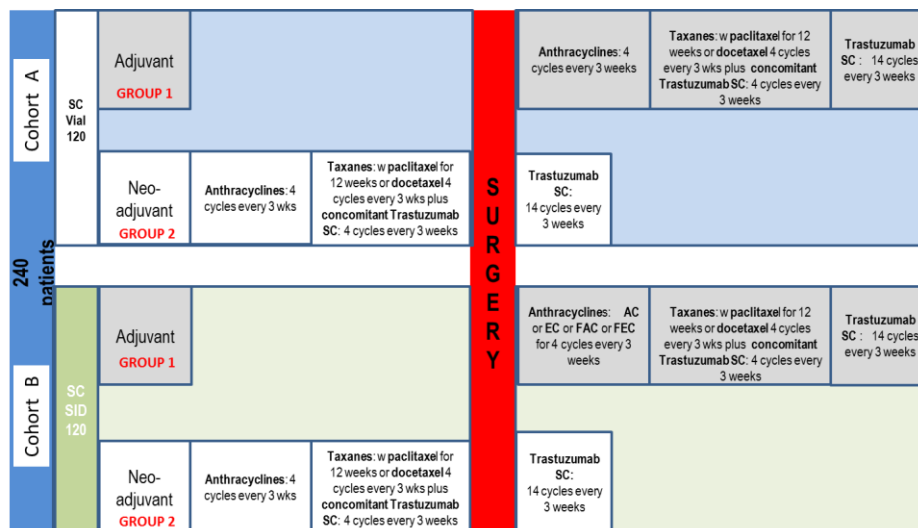
The exploratory secondary objective of the local study is the assessment of PI3K mutation in tumor tissues and in circulating free DNA (cfDNA) in blood.

These assessments will be performed:

- to evaluate the agreement between the PI3K mutation assessment in tumor tissue (gold standard) and in circulating free DNA (experimental)
- to correlate the baseline mutation status (in tumor tissue and cfDNA) with clinical outcome: pathological response to treatment (neoadjuvant arm)
- to correlate the pharmacodynamic change of the cfDNA before and after treatment with clinical outcome.

## 3. STUDY DESIGN

Figure 1: Overview of dosing Schedule



### 3.1 DESCRIPTION OF STUDY

This is a prospective, two-cohort, non-randomized, multicenter, open-label study to assess the safety and tolerability of trastuzumab solution injected

subcutaneously (vial or single-use injection device [SID]) in approximately 240 patients with HER2-positive eBC or LABC who are eligible for anti-HER2 therapy.

The first 120 patients will be treated with trastuzumab SC 600 mg/5ml vial (Cohort A) and the subsequent 120 patients will be treated with trastuzumab SC 600 mg/5ml prefilled single use injection device - SID (Cohort B).

The patients will be enrolled in two sequential cohorts.

In each cohort (A and B), patients will be allocated to adjuvant or neoadjuvant treatment, with pragmatic selection according to conventional clinical criteria and physician choice:

- Group 1= Adjuvant chemotherapy + trastuzumab SC
- Group 2 = Neoadjuvant chemotherapy + trastuzumab SC

In both groups the planned treatment will require sequential chemotherapy regimens comprehensive of Anthracyclines and Taxanes, starting with Anthracycline-containing sequence.

The following drug regimens are allowed:

- AC/EC, 4 cycles (Cycles A1 to A4) → weekly Paclitaxel, 12 wks + trastuzumab 600 mg SC every 3 weeks, 4 cycles (Cycles 1 to 4) → trastuzumab 600 mg SC every 3 weeks, 14 cycles (Cycles 5 to 18)
- AC/EC, 4 cycles (Cycles A1 to A4) → Docetaxel, 4 cycles+ trastuzumab 600 mg SC every 3 weeks, 4 cycles (Cycles 1 to 4) → trastuzumab 600 mg SC every 3 weeks, 14 cycles (Cycles 5 to 18)
- FAC/FEC, 4 cycles (Cycles A1 to A4) → weekly Paclitaxel, 12 wks + trastuzumab 600 mg SC every 3 weeks, 4 cycles (Cycles 1 to 4) → trastuzumab 600 mg SC every 3 weeks, 14 cycles (Cycles 5 to 18)
- FAC/FEC, 4 cycles (Cycles A1 to A4)→ Docetaxel, 4 cycles + trastuzumab 600 mg SC every 3 weeks, 4 cycles (Cycles 1 to 4) → trastuzumab 600 mg SC every 3 weeks, 14 cycles (Cycles 5 to 18)

The regimen selection is based on the physician preference and convenience.

The conventional doses of the selected regimens are detailed in the Appendix 3.

### 3.1.1 ADDITIONAL CHARACTERISTICS OF STUDY DESIGN

Concomitant trastuzumab SC, 600mg administered subcutaneously using either a handheld syringe or SID, starting after the Anthracyclines comprehensive sequences.

The therapy should include a total of 18 cycles/1 year of trastuzumab SC.

Doxorubicin cumulative doses  $\leq 300 \text{ mg/m}^2$  or equivalent for Epirubicin.

Chemotherapy treatment duration, either in the adjuvant and in the neoadjuvant group, of 8 total cycles.



The whole neoadjuvant chemotherapy must be given before surgery.

Surgery after neoadjuvant chemotherapy + trastuzumab SC should include conventional surgical procedures on the breast and on the axilla. SNB (Sentinel lymph node biopsy) is consented in patients with clinically negative axillary status at starting treatment. Surgery after neoadjuvant chemotherapy should be performed 3-4 weeks after the last chemotherapy cycle, or until toxicity, specifically bone marrow toxicity recovery.

Postoperative RT and/or hormonal treatment can be administered concomitantly with trastuzumab SC as adjuvant treatment after chemotherapy, when indicated.

Adjuvant chemotherapy should start within 10 weeks from definite surgery.

Primary chemotherapy should start as soon as possible after study inclusion and no later than 5 working days.

Tissues samples from diagnostic core biopsy and from surgical specimens, as far as blood samples at the planned time points should be collected as reported in the Appendix 1.

The centralization of biological materials (tissues and blood) is a definite prerequisite for the study for the evaluation of PI3K mutations, as well the centralized re-evaluation of HER2 positivity on tissues. The results of HER2 positivity performed centrally will not be required prior to the enrollment into the study.

Safety and efficacy data (DFS and OS) collected in this local study will be transferred to a global Umbrella database for a pooled analysis.

The schedules of mandatory clinical assessments for patients with eBC and for patients with LABC are provided in Appendix 1.

### 3.1.2 LOCAL STEERING COMMITTEE

A local Steering Committee will be established to provide scientific oversight and to ensure that the risk-benefit assessment is maintained during the duration of the trial. The Steering Committee will be made up of Investigators and Roche (the Sponsor) representatives and meet at the regular intervals. A separate Steering Committee charter will outline the committee's composition and members' roles, responsibilities and the frequency of meeting.

### 3.2 LENGTH OF STUDY

The study is estimated to last 5 years from the enrollment of the first patient (18 months of recruitment, 15 months of study treatment (3 months of chemotherapy with anthracyclines + 12 months of trastuzumab in combination with Taxane based chemotherapy) and 2 years of follow-up.

### 3.2.1 TREATMENT DURATION

Patients with eBC will be treated with trastuzumab SC for 1 year, unless intolerable toxicity or investigator-assessed disease progression occurs, or the patient withdraws consent.

### 3.3 SAFETY FOLLOW-UP

All patients will be followed up for 24 months after the last patient has received his/her last study treatment, or earlier, if one of the following is documented: withdrawal from the study, loss to follow-up or death.

### 3.4 END OF STUDY

The end of study is defined as last patient last visit ( LPLV) in the follow-up period.

### 3.5 NUMBER OF PATIENTS

This local (Daughter) study will recruit 240 patients (eBC and LABC) in total.

### 3.6 CENTERS

The study will be performed in approximately 60 oncological centers in Italy.

### 3.7 RATIONALE FOR STUDY DESIGN

Trastuzumab SC is a new administration route that has demonstrated similar PK and efficacy in pCR in the treatment of HER2-positive eBC and LABC in the neoadjuvant setting, during which no new safety signals were identified (Ismael G, Lancet Oncol, 2012).

This is a Phase IIIb, open-label, multinational, multicenter study to assess the safety and tolerability of trastuzumab solution injected subcutaneously (vial or SID) in patients with HER2-positive EBC or LABC. Safety and efficacy data collected in this local (Daughter) study will be transferred to a global database for a pooled analysis.

In this study, the safety and tolerability of trastuzumab SC will be explored, to gain better understanding of the safety profile of trastuzumab SC in the treatment of HER2-positive eBC and LABC patients, whilst addressing more additional scientific questions and investigations.

#### 3.7.1 RATIONALE FOR PATIENT POPULATION

Measurement of HER2 overexpression is a standard of care in determining eligibility for trastuzumab therapy (see the Herceptin® Package Insert). Measurement of HER2 gene amplification has traditionally been performed using IHC measurement. HER2 gene amplification determined by in situ hybridization (ISH) has also proven to be a reliable method for demonstrating HER2-positive

status (Press et al. 2005). Patients whose tumors are positive for HER2 overexpression represent the patient population eligible for study enrollment.

In the current study eBC and LABC patients with HER2 positive tumors will be included.

For more details on rationale for patients with eBC please see Section 1.3.2.

### 3.7.2 RATIONALE FOR POOLING STRATEGY

The data from local studies conducted in various countries will be pooled due to similar designs, endpoints and data structure. A large global database of safety and efficacy data will be created, whilst ensuring these data are collected in a standard, high-quality manner.

Safety and efficacy data will be pooled, summarized and analyzed where appropriate.

### 3.7.3 RATIONALE FOR TEST PRODUCT REGIMEN

The trastuzumab regimen will depend on the patient population and could include mono-or combination therapy.

All eligible patients will receive a fixed dose of 600 mg trastuzumab SC throughout the study, administered q3w (irrespective of body weight) for 1 year, unless intolerable toxicity or investigator-assessed disease progression occurs, or the patient withdraws consent. Known advantages of the use of the fixed dose for all patients and all cycles include a greatly simplified dosing, reduced potential for error, and reduced wastage. The fixed dose of 600 mg of trastuzumab for subcutaneous administration was selected with the aim of achieving trastuzumab serum trough concentrations (C<sub>trough</sub>) that are non-inferior to those obtained with q3w trastuzumab IV administration. Importantly, this dose is consistent with the findings of the BP22023 study (CP2) and identical to that evaluated in the recently reported BO 22227 (HannaH) study.

The regimen consisting of 1 year trastuzumab treatment administered 3-weekly is considered standard of care in patients with eBC, as supported by all major treatment guidelines (NCCN 2011; Goldhirsch et al. 2011; Aebi et al 2011). This 1-year treatment duration is consistent with the current label for trastuzumab IV.

Based on the comparability of the treatment parameters, the efficacy of trastuzumab SC is expected to be similar to that observed in trastuzumab IV trials.

### 3.7.4 RATIONALE FOR SID

Trastuzumab may be supplied as vial or SID. The SID is a single-use injection device for the subcutaneous administration of medicinal products such as trastuzumab SC. At the press of a button, the syringe needle is automatically inserted and the drug is delivered. Upon completion of injection, the needle retracts to prevent handling injuries and visual indication is provided to confirm that the full dose has been delivered. The administration rate is fixed

(approximately 1 mL/min, resulting in a 5-minute injection time) and the dosage delivered is pre-set and controlled at the product manufacturing stage, i.e. 600 mg of trastuzumab formulated with 10,000U of rHuPH20. These attributes ensures a standardized, consistent administration of the medicinal product. The current study is designed to investigate the safety and tolerability of two subcutaneous administration methods for trastuzumab, i.e. assisted administration using a conventional syringe ( vial formulation) and self-administration using a SID. Use of the preloaded SID should reduce preparation time for pharmacy, for clinical staff and might, in the future, enable administration outside a Hospital/ Out patient clinic setting. Use of a SID may also enable self-administration of trastuzumab in the future. This could potentially further improve convenience for patients and compliance with therapy

### 3.7.5 RATIONALE FOR ASSESSMENT OF BIOMARKERS

HER2 potently activates PI3K via heterodimerization with HER3, and trastuzumab down regulates the ligand-independent HER2 dimerization and growth factor signaling cascades downstream of HER2, including the PI3K/AKT/mTOR pathway (Yakes 2002; Nagata, 2004; Junttila, 2009; Mohisin 2005).

Among preclinical models of resistance to trastuzumab, two of the major mechanistic hypothesis behind trastuzumab refractory disease have been changes in the HER2 molecule itself and the activation of the PI3K/AKT pathway. Hyperactivation of the PI3K/AKT/mTOR pathway has been described through several different molecular lesions: loss of the PTEN tumor suppressor, increase of this signal through the activation of HER2-related receptors, such as HER3, or non-HER receptors, such as insulin-like growth factor I receptors (Lu 2001; Sergina 2007), and mutational activation of PIK3CA (Berns 2007).

The gene encoding one of the PI3K catalytic subunits, p110 $\alpha$  (PIK3CA), has been found to be mutated in about 25% of breast cancers. In particular this mutations have been detected in 13-30% of HER2-positive diseases. Most of the reported mutations ( $\geq 80\%$ ) are localized to three hotspots in exons 9 (E542 e E545) and 20 (H1047) of the PIK3CA gene. Exon 20 mutations predominate in breast cancer, in contrast to colorectal cancer where exon 9 mutations predominate (Samuels 2004).

Data from in vitro and in vivo studies suggest that mutations in the PIK3CA gene confer resistance to trastuzumab and that in HER2-overexpressing cancer cells the inhibition of both HER2 and mTOR pathways is required for the optimal antitumor effect of anti HER2 agents (Miller, 2009; Yao, 2009; Junttila, 2009; Garcia Garcia, 2012). HER2+ breast cancer cell lines are highly sensitive to PI3K and mTOR inhibitors before and after acquiring resistance to trastuzumab or lapatinib, suggesting that these drug-resistant cells remain PI3K-dependent.

An increased frequency of changes that activate PI3K/AKT signaling, including in particular PI3KCA mutation, have been reported in trastuzumab-resistant metastatic breast cancer (Chandarlapaty 2012). Retrospective analyses in cohorts of patients with HER2+ metastatic breast cancer (Esteva, 2010; Wang, 2011;

Razis, 2011) have shown that tumors harboring PIK3CA mutations and/or decreased levels of PTEN have a poor outcome following treatment with trastuzumab compared to HER2+ tumors with a 'wild-type' PI3K pathway. Moreover, a neoadjuvant study in patients with HER2+ breast cancer showed that both alterations (PIK3CA mutations and PTEN loss) were associated with a statistically lower pathological complete response rate to trastuzumab with chemotherapy (Dave 2011). To confirm the concurrent importance of these two signals, a few clinical studies suggest that combined targeting of HER2 and the PI3K pathway may be superior to HER2-directed therapy alone (Morrow 2011; André 2010; Jerusalem 2011).

Somatic mutations in the PI3K pathway may than identify cancers with aberrant activation of, and potential dependence on, this signaling pathway providing a biomarker to identify patients unlikely to respond to trastuzumab-based therapy. This hypothesis is however derived from retrospective series and needs to be prospectively confirmed in patients with HER2-positive breast cancer, homogenous for stage of disease.

Availability of biomarkers that predict responses to cancer therapy is instrumental to the rational use of cancer drugs, even though translational studies based on tissue evaluation often suffer because of obvious methodological limitations. Circulating free DNA (cfDNA) has been shown to be present both in circulating tumor cells in blood and as fragments in the plasma of metastatic cancer patients. cfDNA profiles may reflect DNA status in corresponding breast cancer tissues, but results from clinical studies prospectively and specifically addressing these issues are lacking. (van der Auwera, 2009; Board 2010). Minimally invasive blood analyses of cell-free nucleic acid potentially allow repetitive real-time monitoring of events associated with treatment response and relapse and will, therefore, gain clinical utility in the determination of prognosis and treatment efficacy. A recent trial investigated the potential utility of circulating free DNA (cfDNA) as a source for PIK3CA mutation detection in patients with breast cancer. In the metastatic group, where a PIK3CA mutation was present in tumour, the 'pick up' in plasma-derived cfDNA was 80%, even though no PIK3CA mutations were detected in matched cfDNA for early breast cancer cases. (Board, 2010).

These data represents the rational for the sequential and concomitant evaluation of PI3KCA mutation in tissue and in plasmatic cfDNA in breast cancer patients receiving SC trastuzumab in combination with chemotherapy, either in the neoadjuvant and in the adjuvant setting.

### 3.8 OUTCOME MEASURES

#### 3.8.1 EFFICACY OUTCOME MEASURES

The efficacy outcome measures of this study will be to collect data for subcutaneous administration of trastuzumab in the treatment of HER 2-positive eBC and LABC:

- DFS

- OS

Diagnosis of breast cancer relapse will be made based on routine clinical, radiological and laboratory criteria. In case of uncertainty, disease progression should be confirmed by histological or cytological examination of a suspicious lesion, if possible.

In the Neo-adjuvant setting, the activity of two sequential drug regimens, Anthracycline-containing regimen followed by concomitant administration of Taxane and Trastuzumab SC, will be assessed as:

- the incidence of pathological Complete Response in breast and nodes (pCR) (ypT0-is ypN0). Residual in situ disease (ypTis) is considered as pCR.

Laboratory data, vital signs and physical examination data may be summarized.

### 3.8.2 SAFETY OUTCOME MEASURES

The safety outcome measures for this study are as follows:

AEs collection will be the primary endpoint in this study. Summaries will include:

- Incidence and severity by NCI CTCAE version 4.0 of AEs and SAEs
- AEs leading to premature discontinuation of study treatment
- Cardiac safety
  - Cardiac AEs
  - CHF (according to NCI CTCAE version 4.0 and New York Heart Association [NYHA] Classification)
  - LVEF over time. In the event of an asymptomatic decline in LVEF, an algorithm (Appendix 2 in the protocol) will be used to determine whether to continue trastuzumab treatment
- Secondary safety assessments will include the following:
  - Exposure to study medication
  - Duration of treatment, follow-up, and safety observation
  - ECOG
  - Concomitant medications
  - Laboratory data, vital signs and physical examination
  - Premature withdrawals and major protocol violations

The primary analysis will be for all patients. In addition, clinically relevant safety parameters will be analyzed in patient subgroups (eBC neo-adjuvant versus eBC adjuvant, trastuzumab SC monotherapy versus combination with taxanes, etc).

### 3.8.3 PHYSICIAN/PATIENT-SATISFACTION OUTCOME MEASURES

Patient Satisfaction will be assessed by Patient Satisfaction Questionnaire only in Cohort B (use of Trastuzumab SC SID).

In Cohort B, a questionnaire will be completed by patients able to use SID, who completed a minimum of 14 administrations of trastuzumab SC using SID (at least 10 self-administered).

Health Care Professional (HCP) satisfaction will be assessed by a Health Care Professional Questionnaire (HCPQ). A questionnaire will be completed by both the Investigator and a study nurse at each site when at least 4 patients from their site have received at least 5 cycles of adjuvant study treatment. (For those sites that recruit <4 patients the investigator and a study nurse will each complete an HCPQ when last patient at their site has received at least 5 cycles of adjuvant study treatment).

### 3.8.4 EXPLORATORY OUTCOME MEASURES

The focus on translational study is the evaluation of PI3KCA mutations at the most frequent sites (Exon 9, E545K and E542K, and Exon 20, H1047R) in the tumoral bed together with its correlation with the presence of the same mutation in the cfDNA.

Evaluation of PI3KCA mutation in tumor tissues and in blood will be tested in all patients enrolled at the following time points:

- Plasma samples will be drawn at baseline (after eligibility is confirmed, just before the first dose of anthracycline), on treatment pre-Cycle 5 (after first sequence comprehensive of Anthracycline) and on treatment pre-Cycle 9 (after second sequence comprehensive of Taxane and trastuzumab SC).
- Tissue samples will be obtained from pretreatment primary tumor (biopsy material, neoadjuvant group) and from surgical specimens (adjuvant and neoadjuvant groups)

The analysis of PI3K mutation on tissues and on serum cfDNA, as well the centralized re-evaluation of HER2 positivity on tissues, will be performed for care of [REDACTED].

The results of HER2 positivity performed centrally will not be required prior to the enrollment into the study.

The details of biological samples collection are detailed in the Laboratory Manual.

## 4. MATERIALS AND METHODS

### 4.1 TARGET POPULATION

The target population for this study will include patients presenting for the first time with early or locally advanced HER2-positive breast cancer who have not received any previous treatment for invasive malignancy.

The definition of locally advanced breast cancer (LABC) for this study is the following: presence of skin infiltration, irrespective of tumor dimension and/or axillary status (clinical stage T4 N0-3), or extensive axillary involvement, irrespective of tumor dimension or skin infiltration (T1-4, N2-3).

Diagnosis of invasive breast cancer must have been confirmed through a core biopsy.

Furthermore, patients must have given their informed consent and must not meet any of the exclusion criteria detailed in Section 4.3.

## 4.2 INCLUSION CRITERIA

Patients and partners must agree to use a barrier method of contraception during the treatment period and for at least 7 months after the last dose of study drug. Please see Section 5.4.3 for further details.

To be eligible for the study, a patient must fulfill each of the following criteria:

1. Female and male patients aged  $\geq 18$  years
2. Signed informed consent before any specific study procedure
3. Able and willing to comply with protocol
4. Eastern Cooperative Oncology Group (ECOG) performance status 0–1
5. HER2-positive disease immunohistochemistry (IHC)3+ or in situ hybridization (ISH) positive, as determined in a local laboratory that is experienced/certified in HER2-expression testing using an accurate and validated assay
6. Histologically confirmed non-metastatic primary invasive adenocarcinoma of the breast. Stage of disease: T1-4, N0-3, M0.  
T1a-b and pTmic may be included in the presence of at least one of the following unfavorable prognostic factors:
  - clinical( concomitant axillary involvement)  
and/or
  - biological (negative hormonal receptor status and/or high tumor grade and/or young age and/or lymph/vascular invasion and/or high Ki-67)
7. Left ventricular ejection fraction (LVEF) of  $\geq 55\%$  measured by echocardiography (ECHO) or multiple gated acquisition (MUGA) scan prior to first dose of trastuzumab SC
8. Availability of formalin–fixed paraffin-embedded (FFPE) tissue block or partial block from diagnostic core biopsy (only neoadjuvant patients) and from surgical specimens (both adjuvant and neoadjuvant patients), with representative invasive part of the tumor for additional biomarker analysis
9. Intact skin at site of SC injection on the thigh



#### 4.3 EXCLUSION CRITERIA

1. History of other malignancy which could affect compliance with the protocol or interpretation of results Patients with curatively treated carcinoma in situ of the cervix or basal cell carcinoma, and patients with other curatively treated malignancies, other than breast cancer, who have been disease-free for at least 5 years, are eligible
2. Severe dyspnea at rest or requiring supplementary oxygen therapy
3. Concurrent serious diseases that may interfere with planned treatment, including severe pulmonary conditions/illness
4. Serious cardiac illness or medical conditions that would preclude the use of trastuzumab, specifically: history of documented congestive heart failure (CHF), high-risk uncontrolled arrhythmias, angina pectoris requiring medication, clinically significant valvular disease, evidence of transmural infarction on electrocardiogram (ECG), diagnosed poorly controlled hypertension
5. Known infection with human immunodeficiency virus (HIV), active hepatitis B virus (HBV) or hepatitis C virus (HCV)
6. Pregnant or lactating women. Positive serum pregnancy test in women of childbearing potential, premenopausal or less than 12 months of amenorrhea post-menopause, within 7 days prior to first administration of the protocol required chemotherapy treatment.
7. Women of childbearing potential, premenopausal or less than 12 months of amenorrhea post-menopause (unless surgically sterile), and male patients with partners of childbearing potential who are unable or unwilling to use adequate contraceptive measures during study treatment. In this study, menopause is defined as a minimum of 12 consecutive months of amenorrhea during which time no other biological or physiological cause had been identified as a potential cause of this state. Examples of adequate contraceptive measures are intrauterine device, barrier method (condoms, diaphragm) also in conjunction with spermicidal jelly, or total abstinence. Oral, injectable, or implant hormonal contraceptives are not acceptable
8. Concurrent enrolment in another clinical trial using an investigational anti-cancer treatment, including hormonal therapy, bisphosphonate therapy and immunotherapy, within 28 days prior to the first dose of study treatment
9. Known hypersensitivity to trastuzumab, murine proteins, to any of the excipients of Herceptin® including hyaluronidase, or the adhesive of the SC device (for cohort B), or a history of severe allergic or immunological reactions, e.g. difficulty to control asthma
10. No compliance or adherence with the requirements of the protocol
11. Inadequate bone marrow function (as indicated by any of the following):
  - d) Absolute neutrophil count (ANC)  $< 1,500 / \text{mm}^3$  ( $< 1.5 \times 10^9/\text{L}$ )

- e) Platelets  $< 100,000 / \text{mm}^3$  ( $< 100 \times 10^9/\text{L}$ )
- f) Hemoglobin  $< 10 \text{ g/dL}$
- 12. Impaired hepatic function (as indicated by any of the following):
  - d) Serum total bilirubin  $> 1.5 \times$  upper limit of normal (ULN)
  - e) Alanine amino transferase (ALT) and/or aspartate amino transferase (AST)  $> 2.5 \times$  ULN
  - f) Alkaline phosphatase (ALP)  $> 2.5 \times$  ULN
- 13. Inadequate renal function, as indicated by serum creatinine  $> 1.5 \times$  ULN
- 14. Hormonal treatment concomitant with chemotherapy (allowed in adjuvant phase with adjuvant Trastuzumab SC.)
- 15. Pre-existing motor or sensory neuropathy of Grade  $> 1$
- 16. Synchronous bilateral invasive breast cancer

#### 4.4 STUDY TREATMENT

Patients in each cohort (A and B) will be allocated to one of the two treatment Groups, 1 (adjuvant) or 2 (neoadjuvant), according to pragmatic selection, taking into account the conventional clinical criteria, the physician choice and patient convenience.

#### 4.5 TRASTUZUMAB SC DOSES AND ADMINISTRATION

Trastuzumab will be administered subcutaneously with a fixed dose of 600 mg (irrespective of body weight) throughout the treatment phase q3w for 1 year (Cycles 1 to 18).

Trastuzumab administration may be delayed to assess or treat AEs such as cardiac AEs, myelosuppression, or other events, as detailed in Table 2.

No dose adjustment is needed in case of delayed administration of trastuzumab SC as a fixed (600 mg) dose of trastuzumab is given for all subcutaneous cycles in this study.

Dose reductions are not permitted for toxicity. Patients who experience injection-related symptoms may be pre-medicated with paracetamol and antihistamines for subsequent injections.

Trastuzumab will be supplied as a vial for manual administration via hand-held syringe or SID. With either method, trastuzumab will be subcutaneously injected slowly over a period of up to 5 minutes.

- **Vial:** ready to use solution (600 mg trastuzumab/5mL and rHuPH20 10000 units/5 mL) for manual administration using a hand-held syringe
- **SID:** a ready-to-use automated injection device containing 600 mg/5mL trastuzumab and rHuPH20 10000 units/5 mL

Vial must be administered by HCP.

SID might be administered at the hospital by HCP or by self- administration. The first injection will be administered by a trained HCP (physician or nurse). During

the first assisted administration, patients will receive a copy of the Instructions for Use supplied with the SID and personal instructions from a HCP on how to self-administer the study drug. After at least one assisted trastuzumab SC injection using the SID, patients assessed by the investigator as competent to self-administer the study drug using the SID will be allowed to self-administer the remaining trastuzumab SC doses under the direct supervision of a HCP. Patients not deemed competent to self-administer the study drug will have all their trastuzumab SC doses administered by a trained HCP (physician or nurse).

In the event of a device failure, the complaint must be reported to the Sponsor as described in 5.4.4. The device must also be returned via courier to the Sponsor for assessment. Supplemental dosing requirements for the patient will be assessed by the Investigator as per the instructions provided.

Patients in Cohort B should receive treatment with the device as per protocol; however, if a patient refuses treatment, she/he will revert to manual SC administration of trastuzumab for all remaining cycles to complete at least 18 cycles in total as part of the study.

No dose modification of trastuzumab SC will be allowed in any case.

#### 4.6 CHEMOTHERAPY DOSES AND ADMINISTRATION

Chemotherapy doses will be calculated for all drugs according to the body surface (BSA). In calculating BSA, actual weights should be used. No downward adjustments to “ideal” body weight are allowed and the limit of 2.2 m<sup>2</sup> should be used in the few patients who should have a larger calculation of BSA.

Doses of chemotherapy should be modified according to the conventional criteria, by considering side effects intensity and frequency.

Before starting a new treatment cycle, toxicity must have resolved, as specified in the following sections.

Chemotherapy should be administered following trastuzumab SC injection, and as per local Product Information and the investigator's discretion.

Taxane based Chemotherapy and trastuzumab SC are to be given on the same day in a three weekly regimen. Administration of taxane or trastuzumab SC may need to deviate from the planned Schedule e.g. due to adverse event. If the delay in dosing for either drug is foreseen to be 7 days or less, then chemotherapy and trastuzumab should be given together on the same day. In case the dosing delay is more than 7 days, chemotherapy and trastuzumab administration may be uncoupled and given on different days as clinically indicated. However, chemotherapy and trastuzumab should be brought back to a common administration Schedule as soon as possible.

#### 4.7 NEOADJUVANT CHEMOTHERAPY RECOMANDATIONS

Before each treatment cycle, tumor dimensions (largest perpendicular diameters) will be carefully assessed by physical examination.

In the absence of disease progression the chemotherapy program must be continued as planned.

Patients with evidence of local tumor progression (increase of  $\geq 25\%$  in the product of the two largest diameters) will be admitted for surgery as appropriate.

Surgery should be performed within 3-4 weeks from the last dose, according to procedures defined by the local surgeon, who should take into account tumor size and site, breast volume, focality and patient's attitude.

Whenever possible, conservative surgery is preferred.

Sentinel node biopsy (SNB) is considered an acceptable procedure only for patients judged to have an axillary negative nodal status (clinically and/or echographically and/or cytologically detected) before starting neoadjuvant chemotherapy.

Lymph node axillary dissection should be performed preferentially up to the third level. Dissection of the first two levels could be considered. Nodal sampling and the dissection of the first level only cannot be accepted.

All the patients submitted to conservative surgery will receive post-operative irradiation, according to standard procedures.

Patients included into the neoadjuvant group must continue trastuzumab SC treatment at the Scheduled interval even in the peri-operative period ( $\pm 1$  week).

#### 4.8 SYSTEMIC TREATMENT AFTER ADJUVANT-NEOADJUVANT CHEMOTHERAPY

Hormonal therapy in patients with ER and/or PgR-positive disease will be allowed only after adjuvant chemotherapy and therefore rest on the decision of the Participating Center.

All the selected adjuvant hormonal therapies can be given concurrently with trastuzumab SC.

With the purpose of fertility preservation, for adjuvant patients only, LH-RH analogous administration is allowed without any limitation.

#### 4.9 STUDY TREATMENT - IMP

Trastuzumab SC is the investigational medical product (IMP) in this study, according to local approval status and guidelines, supplied as vials and SID formulations.

##### 4.9.1 TRASTUZUMAB SC

The IMP in the SID and in the vials for manual injection, contains 120 mg/mL trastuzumab. The IMP contains 2000 units/mL rHuPH20 (manufactured in a Chinese hamster ovary [CHO] cell line) acting as a permeation enhancer, histidine/histidine-HCl(buffer), alpha, alpha-trehalosedihydrate (bulking agent), methionine (stabilizer), and polysorbate 20 (stabilizer/emulsifier) in water for

injection (WFI) at a pH of  $5.5 \pm 0.5$ . Trastuzumab SC will be provided in the following presentations.

- Ro 045-2317/F06 - Device formulation: Trastuzumab 600 mg/5 mL plus rHuPH20 10000 units/5 mL prefilled SID. Details for equilibration of the device to room temperature can be found in the separate instruction leaflet.
- Ro 045.2317/F07 – Vial for manual subcutaneous injection formulation: Trastuzumab 600 mg/5 mL plus rHuPH20 10000 units/5 mL vial.

According to the Medical Device Directive, the drug/device combination is considered an integral medicinal product and therefore as a single IMP for this study.

The recommended storage conditions are 2-8°C, protected from light. Batch-specific details and information on shelf-life are given in the packaging label. The drug product must not be diluted and should be used according to the instruction leaflet provided separately.

Trastuzumab will be administered subcutaneously with a fixed dose of 600 mg (irrespective of body weight) throughout the treatment phase q3w for 1 year.

Trastuzumab will be supplied as a vial for manual administration via hand-held syringe for the first 120 patients (Cohort A) or SID, for the following 120 (Cohort B). With either method, trastuzumab will be subcutaneously injected slowly over a period of up to 5 minutes.

Trastuzumab for subcutaneous administration will be supplied by Roche. Packaging of trastuzumab for subcutaneous use will be overseen by the Roche Clinical Trial Supplies department. Each IMP unit will bear a label with the identification required by local law, the protocol number, drug identification and dosage. The packaging and labelling of trastuzumab SC will be in accordance with Roche standard and local regulations.

Guidelines for treatment interruption or discontinuation are reported in Table 2 .

#### 4.9.1.1 FORMULATION, PACKAGING AND HANDLING

The study drug will be manufactured and supplied by the Sponsor. Packaging of trastuzumab for subcutaneous use will be overseen by the Roche Clinical Trial Supplies department. Each IMP unit will bear a label with the identification required by local law, the protocol number, drug identification and dosage.

The packaging and labelling of trastuzumab SC (vials and SID) will be in accordance with Roche standard and local regulations.

The study drug must be stored according to the details on the Product Information. The drug label indicates the storage temperature.

Upon arrival of investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals and

temperature conditions, and report any deviations or product complaints to the Monitor upon discovery.

For further details, see the trastuzumab Investigator's Brochure or local prescribing information.

#### 4.9.1.2 INVESTIGATIONAL MEDICINAL PRODUCT ACCOUNTABILITY

The investigational site will acknowledge receipt of IMP, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

The Investigator is responsible for the control of the drugs under investigation. Adequate records for the receipt (e.g. Drug Receipt Record) and disposition (e.g. Drug Dispensing Log) of the IMP must be maintained. Accountability and patient compliance will be assessed by maintaining adequate "drug dispensing" and return records.

Accurate records must be kept for each IMP provided by the sponsor. These records must contain the following information:

- Documentation of IMP shipments received from the sponsor (date received, quantity and batch number)
- Disposition of unused IMP not dispensed to a patient
- A Drug Dispensing Log must be kept current and should contain the following information:
  - Identification of the patient to whom the IMP was dispensed;
  - The date(s), quantity and batch number of the IMP dispensed to the patient.

#### 4.9.1.3 ASSESSMENT OF COMPLIANCE

The Investigator is responsible for ensuring that the study drug is administered in compliance with the protocol. Delegation of this task must be approved by the investigator and clearly documented. Patient compliance will be assessed by maintaining adequate study drug dispensing records. All records and drug supplies must be available for inspection by the Roche Study Monitor at every monitoring visit.

Copies of the dispensing & inventory logs will be retrieved by the Monitor at study end.

#### 4.9.1.4 DESTRUCTION OF THE IMPs

Used and unused IMP will be kept at the site (or designated pharmacy, depending on local practice) for accountability and destruction. Local or institutional regulations may require immediate destruction of used IMPs for safety reasons e.g., cytotoxicity. In these cases, it may be acceptable for the investigational site staff to destroy the dispensed IMP before inspection by the Monitor, provided that source document verification is performed on the remaining inventory and

reconciled against the documentation of quantity shipped, dispensed, returned and destroyed. Written authorization must be obtained from the Sponsor at study start up before destruction of unused trastuzumab SC can take place at a site.

Written documentation of destruction must contain the following:

- Identity (batch numbers and patient numbers) of the IMP(s) destroyed
- Quantity of the IMP(s) destroyed
- Date of destruction (date discarded in designated hazardous container for destruction)
- Method of destruction (the site must provide the Sponsor with documentation of their institutional policy and procedures for handling and disposing of hazardous drugs)
- Name and signature of responsible person who discarded the IMP in a hazardous container for destruction

#### 4.9.1.5 POST-TRIAL ACCESS TO TRASTUZUMAB SC

Roche does not intend to provide trastuzumab SC to patients after conclusion of the study or any earlier patient withdrawal.

### 4.10 CONCOMITANT THERAPY

#### 4.10.1 PERMITTED THERAPIES

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient from screening to the safety follow-up visit. Thereafter only medication applicable for long term reporting must be reported, including breast cancer treatments, anticancer treatment given to treat a recurrence, medication related to the treatment of SAEs that are applicable for long-term reporting. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF). All protocol-allowed medications taken by the patient for concomitant disease(s) should be continued as necessary during the study and be recorded on the eCRF.

Any medication which is necessary for the management of patients ( antiemetic, hematopoietic growth factors, transfusions etc.) must be used at the discretion of the investigator and will be reported in the case report form (CRF).

Concomitant medication permitted may include:

- Paracetamol (acetaminophen) or other analgesics, and diphenhydramine, chlorpheniramine, or other antihistamines used according to local clinical practice for the prevention and treatment of IRR associated with trastuzumab

- Complementary radiotherapy concurrent with trastuzumab SC is consented, provided that in the Adjuvant setting it must be postponed at the end of chemotherapy.
- Adjuvant hormonal treatment after chemotherapy must be given concomitantly with trastuzumab SC, when indicated.
- With the purpose of fertility preservation, for adjuvant patients only, LH-RH analogous administration is allowed without any limitation
- Biphosphonates may be given at the investigator's discretion, to treat documented osteoporosis
- Maintenance therapy for patients with chronic conditions, such as hypothyroidism, hypertension, diabetes, etc.

#### 4.10.2 PROHIBITED THERAPIES

The following treatment are not permitted:

- Concurrent treatment with other systemic HER2-directed immunotherapy
- Concurrent investigational agents of any type
- Hormonal treatment concomitant with neoadjuvant chemotherapy (even with the purpose of fertility preservation).
- Other chemotherapy regimens than those specified at paragraph 3.1.

#### 4.11 STUDY ASSESSMENTS

All patients must provide written informed consent before any study-specific assessments or procedures are performed.

Prior to enrolment in the study, the Investigator will assess each patient with regards to the protocol inclusion exclusion criteria to determine his/her eligibility for the study. Patients must fulfill all the entry criteria for participation in the study.

An Eligibility Screening Form documenting the Investigator's assessment of each patient with regard to the protocol inclusion and exclusion criteria is to be completed by the Investigator.

An Eligibility Screening Failure Log must be maintained by the Investigator.

##### 4.11.1 DESCRIPTION OF STUDY ASSESSMENT

##### 4.11.1.1 MANDATORY PROCEDURE FOR PATIENTS ENROLLMENT

Once a patient has fulfilled the entry criteria, he/she will be assigned a study number in a consecutive order at each center. Each center will also have a center number assigned by the sponsor.

A patient Enrollment and Identification Code list must be maintained by the Investigator.



All the investigation procedures must be performed within 4 weeks prior to first chemotherapy administration with the exception of the baseline breast cancer evaluation with the following timelines:

Neoadjuvant Group.

- Screening radiological examinations to exclude metastatic disease do not need to be repeated if completed within 8 weeks prior to the first chemotherapy administration .
- Bilateral Mammography do not need to be repeated if completed within 6 weeks prior to the first chemotherapy administration.

Adjuvant Group.

- Screening radiological examinations to exclude metastatic disease do not need to be repeated if completed within 8 weeks prior to the first chemotherapy administration
- Bilateral Mammography do not need to be repeated if completed within 6 months prior to the first chemotherapy administration

For the schedule of mandatory clinical assessment please refer to Appendix 1.

#### **NEOADJUVANT GROUP**

Complete history and physical examination with the measure of breast nodule will be performed at baseline. The neoplastic nodule must be marked with a cutaneous tattoo or a clip located under echographic guidance.

Bilateral mammography, with the measurement of tumor size, focality, presence and extension of microcalcifications is required. Any additional conventional methods employed as per local medical practice, such as ultrasound, and Breast MRI are complementary, optional, imaging.

Diagnostic core biopsy of primary tumor is mandatory. It is recommended to use a 14-gauge needle by means of an automated device fired 3-4 times into the lesion to collect sufficient amount of tissue for confirmation of the presence of invasive malignant carcinoma, testing prognostic and predictive indicators and collect tumor specimens.

Histological examination must include:

- Pathological diagnosis of invasive subtype and histological subtype
- Hormonal receptor status (ER and PgR)
- HER2 positivity defined as IHC 3+ or ISH positivity for HER2 cases scored as IHC 2+ as assessed in a local laboratory
- Kinetic indices (Ki67/Mib)
- Tumor grade

Radiological examinations to exclude metastatic dissemination, (at least: chest X-ray, liver ultrasound, bone scan) must be performed. Alternative imaging procedures (TAC, PET) are consented according to the local guidelines.

A twelve lead ECG and evaluation of LVEF by multigated scintigraphic scan (MUGA) or echography will be performed.

LVEF assessments should be performed by either ECHO or MUGA scan: the same imaging technique should be used per patient throughout the study. ECHO should be the method of choice for these assessments. LVEF assessment should be performed as per institutional practice.

Laboratory tests providing measurement of:

- Hematology: hemoglobin, white blood cells and differential, absolute neutrophil count (ANC), platelets count.
- Biochemistry: serum creatinine, urea (BUN), total serum bilirubin, alkaline phosphatase, ALT, AST, sodium, calcium, potassium, glycaemia, albumin.

Pregnancy test for pre and perimenopausal women

### **ADJUVANT GROUP**

Complete history and physical examination with the measure of breast nodule will be registered at baseline.

Bilateral mammography, with the measurement of tumor size, focality, presence and extension of microcalcifications. Breast echography and Breast MRI are complementary, optional imaging.

Histological diagnosis must include:

- Pathological diagnosis of invasive subtype and histological subtype
- Hormonal receptor status (ER and PgR)
- HER2 positivity disease defined as IHC 3+ or ISH positivity as determined in a local laboratory
- Kinetic indices (Ki67/Mib)
- Tumor grade

Pathological disease extension evaluation after surgery must include:

- Tumor size and focality
- Nodal status and total examined nodes
- Margin status for conservatively-treated women
- Report of the eventual skin/ muscle infiltration

Radiological examination to exclude metastatic dissemination, (at least: chest X-ray, liver ultrasound, bone scan) must be performed. Alternative imaging procedures (TAC, PET) are consented according to the local guidelines

A twelve lead ECG and evaluation of LVEF by multigated scintigraphic scan or echography

Laboratory tests providing measurement of:

- Hematology: hemoglobin, white blood cells and differential, absolute neutrophil count (ANC), platelets count.
- Biochemistry: serum creatinine, urea (BUN), total serum bilirubin, alkaline phosphatase, ALT, AST, sodium, calcium, potassium, glycaemia, albumin.

Pregnancy test for pre and perimenopausal women.

Once a patient has fulfilled the entry criteria, he/she will be assigned a study number in a consecutive order at each center. Each center will also have a center number assigned by the sponsor.

A patient Enrollment and Identification Code List must be maintained by the Investigator.

#### 4.11.1.1.1 TIMING OF SCREENING AND PRETREATMENT ASSESSMENTS

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Please see Appendix 1 for the schedule of screening and pretreatment assessments.

#### 4.11.1.1.2 MEDICAL HISTORY AND DEMOGRAPHIC DATA

Medical history includes clinically significant diseases, surgeries, BC disease history (including ER/PgR status, current medications and symptoms), and all medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient starting from the screening visit. The year of start and end date (when applicable) of the past and concomitant treatments, as well the route and dose, will be collected when available.

Demographic data will include date of birth, gender, and self-reported ethnic origin if permitted by local regulations.

#### 4.11.1.1.3 HER 2 STATUS

To be eligible for the study, patients with eBC or LABC must have confirmed HER2- positivity as determined in a local laboratory, defined as one of the following:

- A score of 3+ by ICH
- Gene amplification positive by ISH performed by a validated and approved test in a certified and experienced center.

The re-evaluation of HER2-positivity will be centralized at [REDACTED], [REDACTED].

The results of HER2-positivity performed centrally will not be required prior to the enrollment into the study.

#### 4.11.1.1.4 VITAL SIGNS AND PHYSICAL EXAMINATION

Vital signs assessment includes pulse, blood pressure, body weight, height, and body temperature. Vital signs measurements will be taken while the patient is in a seated position. Height is only measured at Screening.

A general physical exam (including a general neurological exam, as clinically indicated) will be performed. Physical examinations will be performed according to local practice; however, particular attention should be given to the cardiovascular system.

Any abnormality identified at Screening should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits, new or worsened abnormalities should be recorded as AEs on the Adverse Event eCRF.

#### 4.11.1.1.5 PREGNANCY TEST

A serum pregnancy test in women of childbearing potential will be performed within 7 days prior to the first dose of anthracycline. Urine pregnancy testing ~~for~~ should be repeated every 3 months for the duration of study treatment and until at least 7 months after the last dose of study treatment. Any positive urine pregnancy test needs to be confirmed by serum pregnancy test.

#### 4.11.1.1.6 PAST AND CURRENT CONCOMITANT TREATMENTS

All concomitant medications and prior treatments for BC must be reported in the eCRF starting at the Screening visit.

The year of start and end date (when applicable) of the past and current concomitant treatments for eBC, as well as the route and dose, will be collected when available.

#### 4.11.1.1.7 BASELINE EBC DATA

Baseline eBC data will be collected as described in Section 4.12

Diagnosis of BC relapse will be made based on routine clinical, radiological and laboratory criteria. In case of uncertainty, disease relapse should be confirmed by histological or cytological examination of a suspicious lesion, if possible.

#### 4.11.1.1.8 ECOG PERFORMANCE STATUS

To be eligible for the study, patients with eBC or LABC should have ECOG PS 0–1 according to the ECOG PS Scale (Oken et al. 1982).

#### 4.11.1.1.9 MANDATORY SAMPLES FOR STUDY INCLUSION

Tumor samples in the form of formalin-fixed paraffin-embedded tumor block or partial block (16 slides) and blood samples are required for study enrollment.

Tissue samples must be obtained from:

- Pretreatment - primary tumor biopsy material (neoadjuvant group)
- surgical specimens (adjuvant and neoadjuvant groups)

Blood samples must be obtained for all patients at three different time points:

- at baseline (after eligibility is confirmed, before first cycle of anthracycline – pre-Cycle A1 )
- after first sequence comprehensive of Anthracycline (Cycles A1 -A4), before starting trastuzumab SC in combination with taxanes (pre-Cycle1)
- after second sequence comprehensive of Taxane and trastuzumab SC, (pre-Cycle 5)

The modalities of tissue and blood handling and collection are detailed in the specific Laboratory Manual.

Timing of sample collection is reported in the Appendix 1.

During the study (at timepoint decided by the Sponsor), tissues and blood samples must be sent to the central laboratories to perform the analysis of the exploratory biomarkers as well the re-evaluation of HER 2 positivity. The confirmation of Her2-positivity is required to be sure that the correlation of translational analysis and pCR will be performed on the correct HER2-positive population.

#### 4.11.1.1.10 OPTIONAL DONATION OF REMAINING MATERIALS AND CONSENT

The patients will be proposed to donate the remnants of biological samples for future biomarker researches, to the [REDACTED]. The biological samples will be stored in the [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED], under the supervision and responsibility of the [REDACTED].

Specimens for future biomarker research will be collected for patients who give specific consent to participate in this optional research to increase knowledge and understanding of disease biology.

A specific Informed Consent Form will be provided and the investigator will document in the e-CRF whether or not the patient has given consent to donate the sample.

#### 4.11.1.1.11 BASELINE SAFETY DATA

Baseline safety data will be collected as described in section 4.12. Baseline safety data include: AEs and SAEs, cardiac safety (standard 12-lead ECG and LVEF assessments, hematology and biochemistry and concomitant medication.

#### 4.12 CLINICAL ASSESSMENT DURING TREATMENT PERIOD

All patients will be closely monitored for safety and tolerability during all cycles of therapy.

Patients should be assessed for toxicity prior to each dose.

##### 4.12.1 TIMING OF ASSESSMENT DURING TREATMENT

Please see Appendix 1 for the Schedule of assessments performed during the treatment period.

Scheduled study visits are based on a 21-day cycle. All visits must occur within  $\pm$  5 business days from the Scheduled date.

##### 4.12.2 EFFICACY CLINICAL ASSESSMENT

Clinical efficacy assessments and procedures described below will be performed. For the schedule of mandatory efficacy assessments please refer to Appendix1

##### 4.12.3 TUMOR AND RESPONSE EVALUATIONS: BREAST CANCER FOLLOW-UP

**pCR** is the secondary efficacy endpoint for Neo-adjuvant patients in this study. Mammography, with the measurement of residual tumor size, focality, presence and extension of microcalcifications must be repeated for patients included into the neoadjuvant group at the end of treatment, i.e before surgery. For this Group, the intermediate mammography after Anthracycline-containing sequence is optional, but it is recommended. Ultrasound or MRI are optional.

**DFS** is a secondary efficacy endpoint for patients with eBC and LABC in this study. DFS is defined as time from the date of first treatment to the date of local, regional or distant recurrence, contralateral BC or death due to any cause.

Diagnosis of relapse will be made based on routine clinical, radiological and laboratory criteria as described in Appendix 1. Acceptable methods of confirmation of recurrence include radiology, CT scan, brain scan, ultrasound or cytology, as per local practice. In case of uncertainty, disease relapse should be confirmed by histological or cytological examination of suspicious lesion, if possible.

In case of a suspicious recurrence that leads to death quite quickly without having the possibility to confirm relapse of disease, effort should be made to obtain an autopsy report.

##### 4.12.4 ECOG PERFORMANCE STATUS

Performance Status will be evaluated using the ECOG performance Status Scale (Oken et al. 1982).

#### 4.12.5 SAFETY CLINICAL ASSESSMENTS

The following clinical safety assessments and procedures will be performed. For the schedule of safety mandatory assessments please refer to Appendix 1. For full details of safety assessments please refer to section 5.1

##### 4.12.5.1 ADVERSE EVENTS

The National Cancer Institute (NCI) Common terminology for Adverse Events (CTCAE) version 4.0 will be used to evaluate the clinical safety of the treatment in this study. In addition, symptomatic left ventricular dysfunction will be graded according to NYHA classification.

In addition, SAEs occurring during the study will be reported to the Sponsor **within 24 hours** of the investigator becoming aware of them.

For other instruction on documenting and handling AEs please refer to Appendix 1 and Section 5.3

##### 4.12.5.2 VITAL SIGN AND PHYSICAL EXAMINATION

At each cycle, vital signs assessment includes pulse, blood pressure, body weight, height, and body temperature. Vital signs measurements will be taken while the patient is in a seated position. Starting from Cycle 1 blood pressure should be measured pre- and post- trastuzumab administration.

A general physical exam (including a general neurological exam, as clinically indicated) will be performed. Physical examinations will be performed according to local practice; however, particular attention should be given to the cardiovascular system.

New or worsened abnormalities should be recorded as AEs on the Adverse Event eCRF.

##### 4.12.5.3 ELECTROCARDIOGRAMS

A standard 12-lead ECG needs to be performed as specified in Appendix 1, Schedule of Assessment

##### 4.12.3.5.4 LVEF

LVEF assessments should be performed by ECHO or MUGA Scan within 28 days prior to the first trastuzumab SC administration to be eligible for participation in the study and during treatment with trastuzumab SC at Cycles 1, 5, 9, 13 and 17, at safety follow up visit and every 6 months later: the same imaging technique should be used per patient throughout the study. ECHO should be the method of

choice for these assessments. LVEF assessment should be performed as per institutional practice

Symptomatic left ventricular dysfunction (congestive heart failure) will be graded according to NCI-CTCAE version 4.0 and the New York Heart Association functional classification. Any patient who develops clinical signs and symptoms suggesting CHF, with the diagnosis confirmed by a suggestive chest X-ray and a drop in LVEF by ECHO or MUGA will be discontinued from the study medication. CHF should be treated and monitor according to standard medical practice. The incidence of CHF will also be recorded through the study

#### 4.12.5.5 CONCOMITANT MEDICATION

All concomitant medication must be reported in the eCRF starting at the Screening visit. These include:

- Date and extend of primary surgery
- Any loco-regional radiation therapy ( extent or volume and total dose)
- Any hormonal therapy and/or surgical and radiation-induced ovarian ablation and drug induced ovarian suppression (type, drug name, dose and schedule, anticipated duration of therapy)
- Bisphosphonate therapy
- Any additional medication that is necessary for the management of the patient may be used at the discretion of the investigator

All concomitant medications are to be reported until the Safety Follow-up visit. Thereafter, only medication applicable for long-term reporting must be reported, including:

- Breast cancer treatment (e.g., hormonal therapy)
- Anti-cancer treatments given to treat a recurrence
- Medications related to the treatment of SAEs that are applicable for long-term reporting (e.g., treatment of heart failure)

#### 4.12.6 LABORATORY ASSESSMENT

Local laboratory assessments scheduled at day 1 of all cycles must be performed within 72 hours prior to study treatment administration. Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts.

For the schedule of mandatory laboratory assessments please refere to Appendix 1.

##### 4.12.6.1 HEMATOLOGY AND BIOCHEMISTRY

Hematology test including hemoglobin, white blood cells and differential, ANC, platelets count have to be performed at every cycle during chemotherapy, every 4



cycles during administration of trastuzumab SC alone and 4 weeks after last study treatment.

Biochemistry test including serum creatinine, urea (BUN), total bilirubin, alkaline phosphatase, ALT, AST, sodium, calcium, potassium, glycaemia albumin have to be performed at every cycle during chemotherapy, every 4 cycles during administration of trastuzumab SC alone and 4 weeks after last study treatment.

All hematology and blood chemistry laboratory tests will be completed at local laboratories.

#### 4.12.6.2 PREGNANCY TEST

Urine pregnancy testing should be completed as clinically indicated for the duration of study treatment every 3 months (cycle 1, cycle 5, cycle 9, cycle 13, cycle 17). Additional pregnancy testing should be completed as clinically indicated for the duration of the study and until at least 7 months after the last dose of study treatment. Any positive urine pregnancy test needs to be confirmed by serum pregnancy test.

#### 4.13 CLINICAL ASSESSMENTS AT THE SAFETY FOLLOW UP VISIT

Patients who complete the treatment or discontinue from the study early will be asked to return to the clinic 28 days after the last dose of study drug for a safety follow-up visit.

The clinical assessments to be performed at the safety follow-up visit are identical to the assessments during the treatment period except that no treatment drug will be administered.

Please see Appendix1 for the schedule of assessments performed at the safety follow-up visit.

#### 4.14 CLINICAL ASSESSMENTS IN FOLLOW UP VISITS

All patients must be followed for 24 months after the last patient has received his/her last study treatment, according to the Schedule of assessments as outlined in the Appendix 1.

Cardiac assessment at 6, 12, 18 and 24 months ( $\pm 2$  weeks) following treatment cessation will be performed. At these visits, concomitant medication will be recorded, routine breast cancer follow-up will be performed. After the safety follow-up visit, AEs should be collected as outlined in section 5.5 and 5.6.

Please see Appendix1 for the schedule of assessments performed in the follow-up visit.

Conventional clinical and instrumental tests for breast cancer follow up are based on standard guidelines and local policies and they are not considered as study procedures.

After the follow-up visits, patients will be switched to standard treatment, according to Investigator's choice and continue follow-up as recommended in

routine clinical practice (every 6 months to evaluate disease progression and cardiac function).

#### 4.15 FOLLOW-UP ASSESSMENTS

After the safety follow-up visit, AEs should be reported as outlined in section 5.5 and 5.6.

Please see Appendix1 for the schedule of Follow-up assessments.

#### 4.16 ASSESSMENTS OF UNPLANNED VISITS

Assessment other than those specified in Appendix 1, Schedule of Assessment, may be performed, as clinically indicated and need to be adequately documented.

#### 4.17 PATIENT AND HCP SATISFACTION OUTCOMES

Patient Satisfaction will be assessed by Patient Satisfaction Questionnaire (Appendix 5) in Cohort B only.

In Cohort B, a questionnaire will be completed by patients able to use SID, who completed a minimum of 14 administrations of trastuzumab SC using SID (at least 10 self-administered).

Health Care Professional (HCP) satisfaction will be assessed by a Health Care Professional Questionnaire (HCPQ). A questionnaire will be completed by both the investigator and a study nurse at each site when at least 4 patients from their site have received at least 5 cycles of adjuvant study treatment. (For those sites that recruit <4 patients the Investigator and a study nurse will each complete an HCPQ when last patient at their site has received at least 5 cycles of adjuvant study treatment).

#### 4.18 PATIENT, STUDY, AND SITE DISCONTINUATION

##### 4.18.1 PATIENT DISCONTINUATION

The Investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason.

##### 4.18.1.1 DISCONTINUATION FROM STUDY DRUG

Patients must discontinue study drug if any of the following:

- Changes in LVEF (see Appendix 2)
- Pregnancy: a patient must be instructed to stop taking the test “drug” and immediately inform the Investigator if she becomes pregnant during the study.

Other reasons for drug discontinuation are:

- Patient withdrawal of consent at any time

- Any medical condition that the Investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance, specifically defined as non-compliance with the study procedures, the Schedule of assessments or protocol-defined timelines

Patients who discontinue study drug prematurely will be asked to return to the clinic for a safety follow-up visit (see Section 4.13) and has to undergo follow-up assessments (see Section 4.14). The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug prematurely will not be replaced.

#### 4.18.1.2 WITHDRAWAL FROM STUDY

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

#### 4.18.2 STUDY AND SITE DISCONTINUATION

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the Investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonization (ICH) guideline for Good Clinical Practice

## 5. **ASSESSMENT OF SAFETY**

### 5.1 SAFETY PLAN

During the combination treatment, if any of the individual study medications must be delayed for 1 day or more, the trastuzumab should be delayed according to

details reported in section 4.6. Trastuzumab will be administered subcutaneously at a fixed dose of 600 mg regardless of body weight.

#### 5.1.1 GENERAL SAFETY ASSESSMENTS

Patients will be assessed by prior medical history, vital signs (including blood pressure, heart rate, temperature), weight and height (Screening only), physical examination, AEs and concomitant medications. A complete medical history (including demographic profile and prior treatments for cancer) will be documented at Screening.

A general physical exam (including general neurological exam, as clinically indicated) will be performed at screening, every cycle during trastuzumab SC treatment, at the post-treatment safety follow-up visit and subsequently according to the ASCO 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting (Khatcheressian et al. 2006) during the follow-up period (see Appendix 1, Schedule of assessment). During physical examination, particular attention should be given to the cardiovascular system.

Apart from physical exams, subcutaneous injection sites will be checked at every visit and blood pressure will be measured before and after trastuzumab SC administration every cycle, as specified in Appendix 1, Schedule of Assessments.

AEs will be monitored and documented continuously during study (at each 3-weekly treatment visit and during the post-treatment follow-up, as detailed in Section 5.3.1). Serious adverse events (SAEs) will also be monitored, documented and reported; refer to Sections 5.4.2 and 5.5 for details on SAE reporting and follow-up requirements, respectively. All AEs and SAEs (including patients' symptoms and signs of toxicity and clinically significant hematological and biochemical parameters) will be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Changes in concomitant medication will be recorded at each study visit.

Trastuzumab will be given as specified in Section 4.5

Before starting a new treatment cycle, toxicity must have resolved as specified in the following sections.

Trastuzumab SC administration may be delayed to assess or treat AEs such as cardiac AEs, myelosuppression, or other events. No dose reduction will be allowed for trastuzumab SC administration.

#### 5.1.2 CARDIAC SAFETY ASSESSMENTS

Cardiac function will be evaluated regularly throughout the study, by measuring LVEF using echocardiography or MUGA Scan (method selected according to local practice), ECG, and assessment of cardiac signs and symptoms.

For eBC patients and LABC, cardiac safety assessments will be performed at Screening, approximately 3-monthly during trastuzumab SC treatment (at Cycle 1, Cycle 5, Cycle 9, Cycle 13 and Cycle 17; with the results available prior to trastuzumab administration), at the Safety Follow-up visit (LVEF assessment may

occur prior to the day of the Safety Follow-up visit if clinically indicated) and then at 6, 12 and 24 months after treatment cessation and immediately as per Section 5.1.3 in case of cardiac failure; see Appendix 1, Schedule of Assessments.

#### 5.1.2.1 LVEF ASSESSMENT

The Screening LVEF assessment should be performed within 28 days, prior to the first Anthracycline containing regimens administration. To be eligible for participation in this study, patients must have a baseline LVEF  $\geq 55\%$ . The method of assessment (ECHO or MUGA,) is at the Investigator's discretion; however, to the extent possible, the same imaging technique is to be used for each patient throughout the study. The LVEF assessment will be repeated prior to the first trastuzumab SC administration (C1) and subsequently every three cycles. The results must be available before/on the day of the next Scheduled trastuzumab administration, and, should a reduction in LVEF be noticed compared to the pre-trastuzumab treatment start (C1), a decision to give or hold that dose must be made based on the algorithm provided in Appendix 2. In addition, any patient who develops clinical signs or symptoms suspicious of cardiac failure at any time during the study should undergo an LVEF assessment immediately.

Of note, if MUGA Scans are chosen, Investigators must be aware that there may be local guidelines which govern how many MUGA Scans (or the amount of irradiation) a patient is allowed to have in a year, and must ensure that patients are able to adhere to the cardiac assessment Schedule as outlined in Appendix 1. In case additional LVEF assessments become necessary for the medical management of a patient, the Investigator may use echocardiography instead of a MUGA scan to remain within the locally accepted amount of irradiation.

Symptomatic left ventricular dysfunction (congestive heart failure) will be graded according to NCI-CTCAE version 4.0 and the New York Heart Association (NYHA) functional classification (see Appendix 4).

#### 5.1.3 MANAGEMENT OF SPECIFIC AEs

Cardiac safety will be monitored throughout the study, as described in Section 5.1.2. In addition to the Scheduled assessments, any patient who develops clinical signs or symptoms suspicious of cardiac failure at any time during the study should undergo an LVEF assessment immediately. Patients whose LVEF falls  $\geq 10$  percentage points from the value recorded before starting trastuzumab treatment (C1) and to a LVEF  $< 55\%$  may require temporary or permanent cessation of trastuzumab in accordance with the treatment continuation/discontinuation algorithm shown in APPENDIX 2. A repeat LVEF assessment should be performed approximately 3 weeks later. If the LVEF has not improved or has declined further, trastuzumab should be discontinued. All such patients should be referred for assessment by a cardiologist and followed up. Trastuzumab should also be discontinued in any patient who develops clinically significant heart failure.

#### 5.1.4 MANAGEMENT OF SPECIFIC ADVERSE EVENTS

##### 5.1.4.1 DOSE MODIFICATIONS, INTERRUPTIONS AND DELAYS FOR TRASTUZUMAB

Administration of trastuzumab SC may be delayed to assess or treat AEs, as detailed in Table 2.

**Table 2 Action to be Taken in Case of Trastuzumab-Related Toxicity**

<b>Toxicity related to trastuzumab study treatment</b>	<b>Action pertaining to trastuzumab SC*</b>
1. Non-hematological, grade 1 or 2 (excluding cardiac) toxicity	Continue trastuzumab SC therapy
2. Non-hematological, grade 3 or 4 (excluding cardiac) toxicity and toxicity resolved within a maximum of 5 weeks calculated from last planned administration	Hold trastuzumab SC therapy until recovery to grade $\leq 2$ .
3. Non-hematological, grade 3 or 4 (excluding cardiac), toxicity NOT resolved to grade $<2$ or disappeared within a maximum of 5 weeks calculated from last planned administration	Discontinue trastuzumab SC permanently.
4. Recurrence of non-hematological grade 3 or 4 (excluding cardiac) toxicity upon re-challenge	Discontinue trastuzumab SC permanently.
5. Cardiac toxicity: asymptomatic drop in LVEF $\geq 10$ percentage points from Screening and to a LVEF $<55\%$	Trastuzumab SC therapy to be held, continued or resumed according to the algorithm depicted in appendix 2.
6. Cardiac toxicity: symptomatic CHF	Discontinue trastuzumab SC permanently.
7. Cardiac toxicity: other than significant asymptomatic LVEF drop or CHF	Actions must follow rules 1 to 3 for non-hematological toxicities
8. Hematological toxicity	Trastuzumab needs not to be withheld for hematological toxicity

\* Concurrent anti-cancer/endocrine therapy (as applicable) may continue at the Investigator's discretion.

If the patient misses a dose of trastuzumab SC, then the usual maintenance dose should be given as soon as possible, with subsequent maintenance doses given q3w. No dose adjustment is needed in case of delayed administration of

trastuzumab SC as a fixed (600 mg) dose of trastuzumab is given for all subcutaneous cycles in this study.

Dose reductions are not permitted for toxicity. Patients who experience infusion-related or injection-related symptoms may be pre-medicated with paracetamol and antihistamines for subsequent infusions/injections.

In the event of a device failure, the complaint must be reported to the Sponsor as described in 5.4.4. The device must also be returned via courier to the Sponsor for assessment. Supplemental dosing requirements for the patient will be assessed by the Investigator as per the instructions provided.

Patients should receive treatment with the device as per protocol; however, if a patient refuses the patient will revert to trastuzumab SC vial for all remaining cycles to complete at least 18 cycles in total as part of the study.

## 5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including SAEs; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

### 5.2.1 ADVERSE EVENTS

According to the ICH guideline for Good Clinical Practice, an AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

### 5.2.2 SERIOUS ADVERSE EVENTS (IMMEDIATELY REPORTABLE TO THE SPONSOR)

An SAE is any AE that meets any of the following criteria:

- Fatal (i.e., the AE actually causes or leads to death)
- Life threatening (i.e., the AE, in the view of the Investigator, places the patient at immediate risk of death)

This refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe

- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10)
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the Investigators' judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

Serious AEs are required to be reported by the Investigator to the Sponsor within 24 hours after learning of the event (see Section 5.4.2 for reporting instructions).

### 5.2.3 PREGNANCY AND CONTRACEPTION

For patients of childbearing potential and women < 1 year after the onset of menopause, appropriate contraceptive measures are mandatory during study treatment. Examples of adequate contraceptive measures are intrauterine device, barrier method (condoms, diaphragm) also in conjunction with spermicidal jelly, or total abstinence. Oral, injectable, or implant hormonal contraceptives are not acceptable.

Based on PK considerations, contraceptive measures are recommended for at least 7 months following the last dose of trastuzumab.

A patient must be instructed to stop taking the test "drug" and immediately inform the Investigator if she becomes pregnant during the study. The Investigator should report all pregnancies within 24 hours to the Sponsor, using the paper Clinical Trial Pregnancy Reporting Form, [gcp\_for000023]. The Investigator should



counsel the patient, discuss the risks of continuing with the pregnancy, and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

Pregnancies occurring up to 7 months after the completion of trastuzumab must also be reported to the Investigator.

For male patients with a female partner of childbearing potential, cooperation of female partner in accepting the contraceptive methods listed above is required during the study and for at least 7 months following the last dose of study treatment.

Due to potential dual risk of embryo-fetal toxicity (such as oligohydramnios) resulting from systemic exposure to rHuPH20 and trastuzumab, the need for strict adherence to the guidance on contraceptive usage should be reinforced. Should a woman become pregnant during the active treatment phase of a subcutaneous trastuzumab trial her participation should be ended. Should a woman choose to continue with both the pregnancy and trastuzumab treatment, a multi-disciplinary team should closely follow her. There is no evidence to suggest that male exposure to rHuPH20 poses a risk to the developing foetus.

### 5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The Investigator is responsible for ensuring that all AEs (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6. The Investigator is also responsible for reporting medical device complaints (see Section 5.4.4).

For each AE recorded on the Adverse Event eCRF, the Investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

#### 5.3.1 ADVERSE EVENT REPORTING PERIOD

Investigators will seek information on AEs at each patient contact. All AEs, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

**After informed consent** has been obtained **but prior to initiation of study drug**, only SAEs caused by a protocol-mandated intervention should be reported (e.g., SAEs related to invasive procedures such as biopsies).

**After initiation of study drug**, all SAEs/AEs, regardless of relationship to study drug, will be reported until study closure. After this period, the Investigator should report any deaths and serious adverse events. The Investigator is not required to actively monitor patients after the study has ended (see Section 5.6).

Symptomatic congestive heart failure must be reported irrespective of causal relationship during the full course of the study, even if the patient starts a new anticancer regimen.

### 5.3.2 ELICITING ADVERSE EVENT INFORMATION

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all patient evaluation timepoints. Examples of non-directive questions include the following:

“How have you felt since your last clinic visit?”

“Have you had any new or changed health problems since you were last here?”

### 5.3.3 ASSESSMENT OF SEVERITY OF ADVERSE EVENTS

The AE severity grading scale for the NCI CTCAE (v4.0) will be used for assessing AE severity. Table 3 will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

**Table 3 Assessment of AE Severity**

<b>CTC Grade</b>	<b>Equivalent To:</b>	<b>Definition</b>
Grade 1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
Grade 2	Moderate	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living <sup>a</sup>
Grade 3	Severe	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living <sup>b,c</sup>
Grade 4	Life threatening	Life-threatening consequences or urgent intervention indicated <sup>d</sup>
Grade 5	Death	Death related to adverse event <sup>d</sup>

<sup>a</sup> Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

<sup>b</sup> Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

<sup>c</sup> If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of SAE in Section 5.2.2.

<sup>d</sup> Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

#### 5.3.4 ASSESSMENT OF CASUALITY OF ADVERSE EVENTS

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

#### 5.3.5 PROCEDURES FOR RECORDING ADVERSE EVENTS

Investigators should use correct medical terminology/concepts when recording AEs on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one AE term should be recorded in the event field on the Adverse Event eCRF.

##### 5.3.5.1 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

For all AEs a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be

nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

#### 5.3.5.2 ADVERSE EVENTS OCCURRING SECONDARY TO OTHER EVENTS

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by a mild, non-serious infection, only neutropenia should be reported on the eCRF.
- If neutropenia is accompanied by a severe or serious infection, both events should be reported separately on the eCRF.

All AEs should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

Recurrence of breast cancer should not be reported as an AE since this is clearly consistent with progression/relapse of the underlying disease. Hospitalization due solely to the relapse of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of relapse may be reported as AEs if the symptom cannot be determined as exclusively due to the relapse of the underlying malignancy, or does not fit the expected pattern of relapse for the disease under study.

If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

#### 5.3.5.3 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent AE is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent AE is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

#### 5.3.5.4 ABNORMAL LABORATORY VALUES

Not every laboratory abnormality qualifies as an AE. A laboratory test result should be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

#### 5.3.5.5 ABNORMAL VITAL SIGN VALUES

Not every vital sign abnormality qualifies as an AE. A vital sign result should be reported as an AE if it meets any of the following criteria:

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy

- Clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all vital sign findings. Medical and Scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

#### 5.3.5.6 ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST ( $> 3 \times \text{ULN}$ ) in combination with either an elevated total bilirubin ( $> 2 \times \text{ULN}$ ) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, Investigators must report the occurrence of either of the following:

- Treatment-emergent ALT or AST  $> 3 \times \text{ULN}$  in combination with total bilirubin  $> 2 \times \text{ULN}$
- Treatment-emergent ALT or AST  $> 3 \times \text{ULN}$  in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor within 24 hours after learning of the event, either as an SAE or a non-serious AE of special interest (see Section 5.4.2).

#### 5.3.5.7 DEATHS

Deaths that occur before study closure regardless of relationship to study drug, must be recorded on the Adverse Event eCRF (as an outcome) and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of BC. For deaths occurring after this period, please refer to Section 5.6.

A local Steering committee will monitor the frequency of deaths from all causes.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term "**sudden death**" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes

in a patient with or without preexisting heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, “**unexplained death**” should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), “unexplained death” should be replaced by the established cause of death.

During post-study survival follow-up, deaths attributed to progression of eBC should be recorded only on the Survival eCRF.

#### 5.3.5.8 PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the Screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an AE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

#### 5.3.5.9 LACK OF EFFICACY OR WORSENING OF THE UNDERLYING CONDITION

Medical occurrences or symptoms of deterioration that are anticipated as part of the patient’s underlying BC should be recorded as an adverse event if judged by the Investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of BC on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., “accelerated BC”).

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as efficacy assessment data only. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression using objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE.

#### 5.3.5.10 HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 5.2.2), except as outlined below.

The following hospitalization scenarios are not considered to be SAEs:

- Hospitalization for respite care

- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for chemotherapy administration)}
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was Scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease
  - The patient has not suffered an AE
- Hospitalization due solely to progression of the underlying cancer

#### 5.3.5.11 OVERDOSES

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated AE fulfills serious criteria, the event should be reported to the Sponsor within 24 hours after learning of the event (see Section 5.4.2).

### 5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

The Investigator must report the following events to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- SAEs
- Pregnancies
- Device complaints
- Suspected Transmission of Infectious Agents via a Medicinal Product (STIAMP)

The Investigator must report new significant follow-up information for these events to the Sponsor within 24 hours after becoming aware of the information. New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event



Investigators must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

All SAEs regardless of the relationship to the study drug or the time elapsed from the last study drug administration even if the study has been closed, **MUST** be collected and reported. All participating Investigators and the respective independent Ethics Committees (ECs) will be notified of all Suspected Unexpected Serious Adverse Reactions (SUSARs) that are reported during the study. An AE only qualifies as a SUSAR when all of the following conditions are met:

- The event is serious (SAE);
- The event is deemed related to the study drug, according to the criteria provided in Section 5.3.4. (Note: any suspicion of a causal relationship should lead to an assessment of 'related');
- When assessed against the known safety profile of trastuzumab SC (as described in the IB), the event is considered unexpected (not foreseen in the IB).

When all patients at a particular site are off treatment as defined by the protocol:

- Individual SUSAR reports originating in that particular trial will be forwarded to all participating Investigators and the IECs associated with their sites, on an expedited basis;
- Individual SUSARs considered to be a significant safety issue and/or which result in Roche recommending a change to the Informed Consent Form (ICF), will be reported in an expedited manner to all Investigators and reviewing IECs;
- SUSAR reports originating from other trials using the same IMP will be provided as six-monthly SUSAR Reports (SSRs) to all Investigators and IECs where long-term follow-up studies are carried out.

#### 5.4.1 EMERGENCY MEDICAL CONTACTS

##### **MEDICAL MONITOR (ROCHE MEDICAL RESPONSIBLE) CONTACT INFORMATION**

The Investigators involved in the study will receive a toll-free number for an Emergency Medical Call Centre to be used for study related medical emergencies. This number is intended to be used for emergencies outside the normal working hours or when the regular medical contact for the study cannot be reached.

The Call Centre is manned 24 hours a day/7 days per week/52 weeks per year by an outside vendor, who will access the appointed **Medical Responsible (MR)** for each ongoing study directly from a Roche portal (GCP Resource Center, 24-hr Medical Emergency Physicians Contact,

<http://gcpcenter.roche.com/synergy/portal/view/pdq-spi/gcpcenter/34-64711453/>).

The people at the Call Centre are not medically trained and will not provide any medical information; rather, they will contact the Medical Responsible (Duty Doctor) at [REDACTED], and connect them to the investigator.

For each study, several MR are appointed providing a robust escalation matrix.

#### 5.4.2 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS

For reports of SAEs, Investigators should report to Roche all case details that can be gathered, within 24 hours after learning, completing the paper SAE Reporting Form and faxing it to the SAE Responsible, using the fax numbers reported into the SAE Cover Sheet which is to be faxed along with SAE report form.

All information concerning the SAEs should also be reported into e-CRF.

#### 5.4.3 REPORTING REQUIREMENTS FOR PREGNANCIES

##### 5.4.3.1 PREGNANCIES IN FEMALE PATIENTS

For women of childbearing potential (defined as pre-menopausal, less than one year after the onset of menopause or not surgically sterilized), appropriate contraceptive measures are mandatory during study treatment (see Section 5.2.3). Based on PK considerations, contraceptive measures are recommended for at least 7 months following the last dose of trastuzumab.

Female patients of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 7 months after the last dose of study drug. A paper Pregnancy Report Form should be completed and faxed to SAE Responsible within 24 hours after learning, using the fax numbers reported into the Pregnancy Cover Sheet which is to be faxed along with SAE report form. The Investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

##### 5.4.3.2 PREGNANCIES IN FEMALE PARTNERS OF MALE PATIENTS

Male patients will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant during the study or within 7 months after the last dose of study drug. A paper Pregnancy Report worksheet should be completed and faxed to SAE Responsible within 24 hours after learning, using the fax numbers reported into the Pregnancy Cover Sheet which is to be faxed along with SAE report form. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the Investigator will update the Pregnancy Report with additional information on the

course and outcome of the pregnancy. An Investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

#### 5.4.3.3 ABORTIONS

Any spontaneous abortion should be classified as a SAE (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the paper SAE Reporting Form, and reported to the SAE Responsible within 24 hours after learning of the event (see Section 5.4.2).

#### 5.4.3.4 CONGENITAL ANOMALIES/BIRTH DEFECTS

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as a SAE, recorded on the paper SAE Reporting Form, and reported to the SAE Responsible within 24 hours after learning of the event (see Section 5.4.2).

#### 5.4.4 REPORTING REQUIREMENTS FOR MEDICAL DEVICE COMPLAINTS

The Investigator must report all medical device complaints to the SAE Responsible. The Investigator should document as much information as possible on an e-mail to be sent to the SAE responsible, including the product batch number and expiration date. If the medical device complaint results in an adverse event, the paper Medical Device (MD) Complaint Form must be completed and reported to SAE Responsible within 24 hours after learning of the event. The adverse event must be reported on the Adverse Event eCRF. If the event is serious, beside the e-mail a SAE form should be faxed to Safety Responsible within 24 hours after learning of the event, as outlined in Section 5.4.2.

### 5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

#### 5.5.1 INVESTIGATOR FOLLOW-UP

The Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the patient is lost to follow up, or the patient withdraws consent. Every effort should be made to follow all SAEs until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

After the 28 day period following the last dose of trastuzumab in an individual patient, AE follow-up will continue as follows:

**RELATED AEs AND SAEs** will be followed until one of the following occurs:

- Resolved or improved to baseline state
- Investigator confirms that no further improvement can be expected
- Start of a new anti-cancer regimen
- Death

**UNRELATED SEVERE OR LIFE THREATENING AEs AND SAEs** will be followed until one of the following occurs:

- Resolved or improved to baseline state
- Severity improved to Grade 2
- Investigator confirms that no further improvement can be expected
- Start of new anti-cancer regimen
- Death

**UNRELATED GRADE 1 OR GRADE 2 AEs** will be followed until 4 weeks after the last dose of study drug in an individual patient.

The final outcome of each adverse event must be recorded on the eCRF.

#### **FOLLOW-UP OF ABNORMAL LABORATORY TEST VALUES**

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range or baseline state and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF.

#### **5.5.2 SPONSOR FOLLOW-UP**

For SAEs and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

#### **5.6 POST-STUDY ADVERSE EVENTS**

At the safety follow-up visit, the Investigator should instruct each patient to report to the Investigator any subsequent adverse events. The Sponsor should be notified if the Investigator becomes aware of any death or serious adverse event occurring at any time, after a patient has discontinued study participation, even after study closure, regardless of relationship to treatment of study drug. The Investigator is not required to actively monitor patients after the study has ended.

The Sponsor should also be notified if the Investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study.

The Investigator should report these events to Roche Safety Risk Management on the Adverse Event eCRF. If the Adverse Event eCRF is no longer available, the Investigator should report these events, **indefinitely**, directly to Roche Safety Risk Management via telephone (see "Protocol Administrative and Contact Information & List of Investigators").

#### 5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Trastuzumab Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

## 6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The following is an outline of the statistical methodology that will be used to report and analyze this study. A more detailed description will be provided in a separate statistical analysis plan (SAP) that may include additional exploratory analysis not explicitly mentioned in the following sections.

Local safety and efficacy data will be transferred to a global database and will be pooled for analysis. These data will also be analyzed in subgroups according to study design, patient population, and other relevant factors. The Intent-to-Treat (ITT) population will be defined as all enrolled patients. The modified-Intent-to-Treat (m-ITT) population will be defined as all enrolled patients satisfying inclusion and exclusion criteria for eligibility. All baseline summaries will be based on the ITT, while efficacy analyses will be based on the m-ITT population.

All safety summaries will be based on the safety population, defined as all recruited patients who receive at least one dose of study medication (trastuzumab SC)

Where it is stated that data will be summarized, unless alternative methods are given, the following will apply:

- continuous data will be summarized using: mean, median, range, standard deviation and standard error

- discrete data will be summarized using frequency counts and percentages

## 6.1 DETERMINATION OF SAMPLE SIZE

The study focuses on a sample of patients eligible for adjuvant and neoadjuvant chemotherapy + trastuzumab SC.

Patients will receive treatment according to the following schema, which are usually adopted in clinical practice.

- A) Neoadjuvant: CT x 4 cycles → CT+Trastuzumab SC x 4 cycles → Surgery → Trastuzumab SC x 14 cycles
- B) Adjuvant: Surgery → CT x 4 cycles → CT+Trastuzumab SC x 4 cycles → Trastuzumab SC x 14 cycles

Since the chemotherapy amount of treatment is expected to be the same in the two groups, it is reasonable to expect the same incidence of side effects.

For the purpose of the estimation of the sample size, the LVEF rate has been chosen as the safety endpoint of primary interest. The tables provide the resultant confidence intervals for various sample sizes and various event rates, according to the assumptions derived by NOAH study (ref.) Assuming an observed LVEF Grade ≥ 1 rate of 25%, a LVEF Grade ≥ 2 of 4% and a LVEF Grade ≥ 3 of 2% a sample size of 240 will produce a 95% confidence interval deemed sufficiently precise to draw valid conclusions around the event rate. Safety results within each treatment group will be useful for descriptive purpose. The estimation of the confidence intervals will be performed using SAS based on Clopper-Pearson methodology.

**Table 4** Clopper-Pearson 95% Confidence Intervals for the incidence of different LVEF Grade

Number of Patients	LVEF Grade: Estimated Indicence		
	≥3: 2%	≥2: 4%	≥1: 25%
50	0.1% - 10.6%	0.5% - 13.7%	14.6% - 40.3%
190	0.6% - 5.3%	1.8% - 8.1%	19.3% - 32.1%
240	0.7% - 4.8%	2.0% - 7.5%	19.7% - 31.0%

## 6.2 SUMMARIES OF CONDUCT OF STUDY

This is a phase III prospective, two-cohort, non-randomized, multi-centre, national, open label study. Eligible patients with HER2-positive eBC and LABC will be allocated to one of two cohorts:

- Cohort A (approximately 120 patients) will receive trastuzumab SC by assisted administration using a conventional syringe.
- Cohort B (approximately 120 patients) will receive trastuzumab SC, first assisted, then self-administered using a SID.

Patients in both cohorts will receive a total of 18 cycles of trastuzumab SC, unless disease recurrence, unacceptable toxicity or patient withdrawal necessitates earlier treatment cessation. During adjuvant / neoadjuvant therapy, patients will be assessed for safety and efficacy, as detailed in Appendix 1.

Safety endpoints are the primary objectives in this study.

Secondary efficacy endpoints include pCR (only neoadjuvant Group), DFS, OS, patients' satisfaction with trastuzumab SC administration using the SID (Cohort B patients who went on to self-administration only) and HCP satisfaction.

The primary analysis of safety endpoints, the analysis of efficacy (pCR) and the analysis of efficacy (DFS, OS) will take place when all patients have received 18 cycles of trastuzumab SC and have completed the post-treatment Safety Follow-up assessments. The final analysis with the summaries for safety parameters will be performed when the last patient has been followed up for at least 24 months after her/his last study treatment, or earlier, if one of the following is documented for all treated patients: withdrawal of consent, loss to follow up or death. This is expected to take place approximately 5 years after the enrolment of the first patient, based on an expected 18-month recruitment period per cohort, 15 months of study treatment and 2 years of follow-up after the last study treatment of the last patient. There will be no adjustments for multiplicity of endpoints or within-subgroups comparisons.

A Clinical Study Report (CSR) will be written at the time of the primary endpoint analysis, and distributed to Health Authorities in keeping with the applicable regulatory requirements. All subsequent data analyses will be reflected in an addendum to the CSR.

In order to assess the conduct of the study, major protocol violations will be summarized and listed. Such violations will be defined prior to the first reporting event but will include at least the following:

Non compliance with inclusion criteria

- Non compliance with exclusion criteria
- Non compliance with study treatment
- Use of disallowed concomitant medication

### 6.3 SUMMARIES OF BASELINE CHARACTERISTICS

All demography and baseline disease characteristics (collected at either the Screening or Baseline visits) will be summarized using the ITT population. Summaries will include:

- Demography (age, gender, weight)
- HER2 determination

- Medical History (including BC Disease History)
- Pregnancy Test Results
- Prior Medications

## 6.4 EFFICACY ANALYSES

The efficacy endpoints will be analysed using the m-ITT population.

The secondary efficacy endpoint for neo-adjuvant setting will be pCR in breast and in nodes (ypT0 is ypN0). Residual in situ disease (ypTis) is considered as pCR. According to the literature data, the expected rate of pCR will be about 35-40%. (Gianni L, 2008).

The response rate will be presented as proportion with relative confidence intervals.

As far as the other efficacy endpoint is concerned ,OS is defined as the time from baseline visit until death from any cause. Patients still alive at the time of analysis and patients who are lost to follow-up will be censored at their last time known to be alive.

DFS is defined as the time from baseline visit until first documented disease or death, whichever comes first. Patients who have no disease and have not died or who are lost to follow-up at the time of analysis will be censored at the date of the last tumor assessment where no disease was documented or the last date of follow-up for disease, whichever is last. Patients without post baseline tumor assessments will be censored at the time of their baseline visit unless death occurs prior to their first scheduled tumor assessment.

The analysis of OS and DFS will be estimated using Kaplan-Meier methodology and summarized using the 25th and 75th percentiles, the median survival and a 95% confidence interval for the median. The plot of Kaplan-Meier estimates for the single treatment group will be presented.

## 6.5 SAFETY ANALYSES

AEs collection will be the primary endpoint in this study. Summaries to be produced will include:

- Incidence and severity by NCI CTCAE version 4.0 of AEs and SAEs
- AEs leading to premature discontinuation of study treatment
- Cardiac safety
  - Cardiac AEs
  - CHF (according to NCI CTCAE version 4.0 and New York Heart Association [NYHA] Classification)



- LVEF over time. In the event of an asymptomatic decline in LVEF, an algorithm (Appendix 2 in the protocol) will be used to determine whether to continue trastuzumab treatment
- Secondary safety assessments will include the following:
  - Exposure to study medication
  - Duration of treatment, follow-up, and safety observation
  - ECOG
  - Concomitant medications
  - Laboratory data, vital signs and physical examination
  - Premature withdrawals and major protocol violations

The safety summaries will be based on the safety population defined as all enrolled patients who received at least one dose of study medication.

AEs will be coded centrally by the Sponsor using the latest MedDRA dictionary and summarized by body system and preferred term.

Summaries will include frequency counts and percentages. For certain AEs (or groups of AEs) of interest, e.g. Cardiac AEs, 95% confidence intervals for incidences will be provided. Confidence intervals will be calculated using Clopper-Pearson methodology.

Summaries will include:

- The incidence of AEs and SAEs
  - overall
  - by severity using NCI CTCAE version 4.0
  - by relationship to study drug
- The incidence of AEs leading to premature discontinuation of study treatment
  - overall
  - by severity using NCI CTCAE version 4.0
  - by relationship to study drug
- The incidence of specific Cardiac AEs and SAEs
  - overall
  - by severity using NCI CTCAE version 4.0
  - by relationship to study drug

These adverse event summaries will be based on treatment emergent adverse events (those events starting on or after first study drug and within 28 days after

last study drug). Similar summaries for the safety follow-up period (starting after 28 days after last study drug and continuing to study end) will be produced. AEs and SAEs occurring prior to first study drug will be listed only.

Cardiac monitoring (12-lead ECG and LVEF) will be summarized by cycle including change from baseline summaries where appropriate.

Exposure to study treatment will be summarized overall and by cycle. Summary measures will include:

- days on drug
- total daily dose
- cumulative dose

Duration of the treatment period will be summarized in both days and cycles.

Duration of safety follow-up will be summarized in days.

Vital signs will be summarized by cycle including change from baseline as appropriate.

Concomitant medications will be coded centrally by the Sponsor using the latest INN (International Nonproprietary Name) dictionary and summarized during the treatment phase by super class term and preferred term.

Anti-cancer treatments given to treat a recurrence will also be summarized during safety follow-up.

Hematology and serum chemistry results will be summarized by cycle including change from baseline as appropriate. For laboratory parameters where CTC grading is available, shift tables and change from baseline to worst on-treatment value will be produced.

## 6.6 PATIENT-SATISFACTION OUTCOME ANALYSES

Patient's Satisfaction with trastuzumab SC administration using the SID will be evaluated for patients who went on self-administration only.

Data derived from the questionnaires regarding patients satisfaction will be presented as proportion with relative 95% confidence intervals.

## 6.7 HCP-SATISFACTION OUTCOME ANALYSES

The 'HCP satisfaction with SC trastuzumab' will be assessed by the following questions on the HCPQ:

- I. "All things considered, do you think neo/adjuvant Herceptin SC administration is a valid option considering the patients advantages?"

- II. “All things considered, do you think neo/ adjuvant Herceptin SC administration is a valid option considering the department organization/simplification?”

At each site, the investigator and a study nurse will complete a HCPQ after 4 patients have received at least 5 cycles of adjuvant study treatment. (For those sites that recruit <4 patients the investigator and a study nurse will each complete an HCPQ when last patient at their site has received at least 5 cycles of adjuvant study treatment).

Data derived from the questionnaires regarding HCP satisfaction will be presented as proportion with relative 95% confidence intervals.

## 6.8 EXPLORATORY ANALYSES

For the analysis of translational study, the association of PI3K mutation status at baseline and pCR (neoadjuvant arm) will be assessed by means of a univariate and multivariate logistic regression analysis, where the odds of pCR will be modeled as function of the marker and adjusted by baseline factors relative to tumor and patients characteristics.

The association between the pharmacodynamic change of the assessment for the PI3K mutation status in cfDNA pre and post treatment and pCR will be performed as described below. The cut-off value for statistical significance will be set  $\alpha=0.05$  two tails.

A comparison between PI3K mutation assessment in tumor tissue collected at baseline (core biopsy and tumor blocks in the neoadjuvant and adjuvant arm respectively) (gold standard assessment) and the assessment of PI3K mutation in cfDNA (experimental assessment) will be performed and consistency will be assessed by  $\kappa$  statistic.

Sensitivity, specificity, positive and negative predictive value and overall agreement for the experimental assessment will be calculated.

Correlative studies will be performed according to the following clinical outcome:

- the achievement of pathological complete response (pCR) of invasive tumor in breast and axilla (in situ residual disease allowed). Patients progressed under treatment or for which surgery will not be feasible at the end of treatment will be considered as not having achieved a pCR.
- the association between clinical outcomes (pCR) and the baseline assessment of the PI3K mutation status as defined in tumor samples or cfDNA will be performed.
- the pharmacodynamic changes of the PI3K mutation assessment in cfDNA by comparing the pharmacodynamic changes and clinical outcome (pCR) will be performed.

The analysis of efficacy secondary end points will be conducted according both to local and to central HER2 evaluation, while the translational evaluations will be conducted only on the central HER2 positive cases.

All analyses will be described on the overall population of interest and broken down by relevant characteristics of patients and disease, where deemed appropriate.

## 6.9 INTERIM ANALYSES

The primary analysis will be undertaken once all patients have completed the study (treatment phase and 28-days safety follow-up visit). In addition to this primary analysis there will be annual interim analysis for safety reporting and presentation of safety and efficacy results. These annual reporting events will start 1 year after first visit and end when the last patient has finished follow-up.

# 7. DATA COLLECTION AND MANAGEMENT

## 7.1 DATA QUALITY ASSURANCE

Data management will be performed by a CRO.

The Sponsor will supply eCRF specifications for this study. A contract research organization (CRO) will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will produce a Data Quality Plan that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the CRO, using the CRO standard procedures to handle and process the electronic transfer of these data.

Roche will perform oversight of the data management of this study, including approval of the CRO data management plans and specifications. Data will be periodically transferred electronically from the CRO to Roche, and Roche's standard procedures will be used to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO standard procedures.

Roche will ensure the quality of safety and efficacy data to be transferred to the global database.

## 7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to Roche and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the Investigator or a designee.

At the end of the study, the Investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

## 7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5

To facilitate source data verification, the Investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable health authorities.

## 7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the

original data as well as the reason for the change, name of the person making the change, and date of the change.

## 7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, questionnaire data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

## 8. ETHICAL CONSIDERATIONS

### 8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

### 8.2 INFORMED CONSENT

Roche sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from Roche sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to Roche for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed

consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

### 8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.5).

In addition to the requirements for reporting all AEs to the Sponsor, Investigators must comply with requirements for reporting SAEs to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site study file.

### 8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any the Sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, the Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

## 8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

# 9. **STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION**

## 9.1 STUDY DOCUMENTATION

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the Investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

## 9.2 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The Investigator will permit national and local health authorities, The Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

## 9.3 ADMINISTRATIVE STRUCTURE

The study will have a local Steering Committee.

IxRS and eCRF will be conducted by a contract research organization (CRO) together with the Sponsor.



Assessment of laboratory test results will be performed locally.

#### 9.4 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of the Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate the Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

#### 9.5 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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# APPENDIX 1

## Schedule of Assessments

### NEOADJUVANT PATIENTS

	Screening	Baseline	Pre-Surgery Treatment Period					Surgery	Post-Surgery Treatment Period								Safety Follow-up	Follow-up visits
Day  (Treatment Cycle #)	-28 to 1	-7 to 1	Anthracycline containing regimens			Starting trastuzumab (+ taxanes)			Trastuzumab ± RT ± hormonal therapy								4 weeks after last study treatment	Continuing for 24 months after safety follow (months 6,12,18,24)
			A1	A2, A3	A4	1	2, 3, 4		5	6, 7, 8	9	10, 11, 12	13	14, 15, 16	17	18		
Explain study and obtain signed Informed Consent [a]	x																	
Demographics and medical history [b, c]	x																	
HER2 determination [d]	x																	
Review inclusion/exclusion criteria	x																	
Baseline Breast Cancer evaluation [e]	x																	
Vital signs, physical examination [f], weight, and height [g]	x	x	x	x	x	x	x		X	x	x	x	x	x	x	x		
ECOG performance status	x		x			x			x		x		x		x		x	x
Cardiac monitoring [h, p]  12-lead ECG LVEF Signs/symptoms	x x x					x x x			X X X		x x x		x x x		x x x		x x x	x x x



	Screening	Baseline	Pre-Surgery Treatment Period					Surgery	Post-Surgery Treatment Period								Safety Follow-up	Follow-up visits
Day (Treatment Cycle #)	-28 to 1	-7 to 1	Anthracycline containing regimens			Starting trastuzumab (+ taxanes)			Trastuzumab ± RT ± hormonal therapy								4 weeks after last study treatment	Continuing for 24 months after safety follow (months 6,12,18,24)
			A1	A2, A3	A4	1	2, 3, 4		5	6, 7, 8	9	10, 11, 12	13	14, 15, 16	17	18		
Pregnancy test [i]		x				x			x		x		x		x			x
Hematology and biochemistry [j]	x		x	x	x	x	x		x		x		x		x		x	
Biomarkers blood sample collection *			x*			x*			x*									
Tissue collection **		x						x										
Routine breast cancer follow-up [k]	x				x <sup>i</sup>	x <sup>i</sup>		x <sup>i</sup>	Assessment as per institutional practice or ASCO adjuvant follow-up Guidelines 2006 to be reported 6 monthly									
AEs and SAEs [l]	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x	x	x
Surgery including Pathological Response Assessment [o]								x										
Past and Concomitant medications [m]	x	x	x	x	x	x	x		x	x	x	x	x	x	x	x		x <sup>i</sup>
Anthracycline-containing regimen			x	x	x													
Taxane						x	x											
Trastuzumab [n]						x	x		x	x	x	x	x	x	x	x		

## ADJUVANT PATIENTS

	Screening	Baseline	Treatment Period													Safety Follow-up	Follow-up visits
Weeks  (Treatment Cycle #)	Days -28 to -1	Days -7 to -1	Anthracycline containing regimens			Starting trastuzumab (+ taxanes)		Trastuzumab ± RT ± hormonal therapy								4 weeks after last study treatment	Continuing for 24 months after safety follow (months 6,12,18,24)
			A1	A2, A3	A4	1	2, 3, 4	5	6, 7, 8	9	10, 11, 12	13	14, 15, 26	17	18		
Explain study and obtain signed Informed Consent [a]	x																
Demographics and medical history [b, c]	x																
HER2 determination [d]	x																
Baseline Breast Cancer evaluation [e]	x																
Review inclusion/exclusion criteria	x																
Vital signs, physical examination [f], weight, and height [g]	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x		
ECOG performance status	x		x			x		x		X		x		x		x	x

	Screening	Baseline	Treatment Period													Safety Follow-up	Follow-up visits
Weeks (Treatment Cycle #)	Days -28 to -1	Days -7 to -1	Anthracycline containing regimens			Starting trastuzumab (+ taxanes)		Trastuzumab ± RT ± hormonal therapy								4 weeks after last study treatment	Continuing for 24 months after safety follow (months 6,12,18,24)
			A1	A2, A3	A4	1	2, 3, 4	5	6, 7, 8	9	10, 11, 12	13	14, 15, 16	17	18		
Cardiac monitoring [h, p]																	
12-lead ECG	x					X		x		X		x		x		x	x
LVEF	x					X		x		X		x		x		x	x
Signs/symptoms	x					X		x		X		x		x		x	x
Pregnancy test [i]		x				x		x		x		x		x			x
Hematology and biochemistry [j]	x		x	x	x	x	x	x		X		x		x		x	
Biomarkers blood sample collection *		x				x*		x*									
Tissue collection **		x															
Routine breast cancer follow-up [k]	x		Assessment as per institutional practice or ASCO adjuvant follow-up Guidelines 2006 to be reported 6-monthly														
AEs and SAEs [l]	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x
Past and Concomitant medications [m]	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x <sup>i</sup>
Anthracycline-containing regimen			x	x	x												
Taxane						x	x										
Trastuzumab [n]						x	x	x	x	X	x	x	x	x	x		

AE = adverse event, ASCO = American Society of Clinical Oncology, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, LPLV = last patient last visit, LVEF = left ventricular ejection fraction, PK = pharmacokinetic, SAE = serious adverse event, SC = subcutaneous  
First dose of drug = study cycle 1, Day 1. A treatment period is approximately 3 months in duration, i.e. 4 treatment cycles. Assessments can also be performed more frequently if clinically indicated.

## Notes

- [a] Written Informed Consent must be obtained before any study-specific assessments or procedures are performed
- [b] Demographic data including date of birth, gender, and self-reported ethnic origin where permitted by local regulations
- [c] Breast cancer disease history, including ER/PgR status, prior anticancer treatments, current medications and symptoms
- [d] HER2-positivity is defined as immunohistochemistry (IHC)3+ or gene amplification by in situ hybridization (ISH)
- [e] Baseline breast cancer evaluation to be completed within 4 weeks before protocol related chemotherapy treatment start, with the following exceptions: Screening radiological examinations to exclude metastatic disease (chest X-ray, liver ultrasound, bone scan) do not need to be repeated if completed within 8 weeks prior to the first chemotherapy administration; Bilateral Mammography do not need to be repeated if completed within 6 weeks prior to the first chemotherapy administration.
- [f] Vital signs and physical examination including pulse, blood pressure, and body temperature are measured at Screening, at every treatment cycle, and at the Safety Follow-up visit
- [g] Weight is measured at baseline, at every treatment cycle, at the Safety Follow-up visit, and at each visit during follow-up period. Height is only measured at Screening
- [h] LVEF assessments by either ECHO or MUGA Scan: the same imaging technique should be used per patient throughout the study. Echocardiography should be the method of choice for these assessments. LVEF assessment is mandatory at Screening. During treatment, a 3-monthly assessment should be performed or as per institutional practice and immediately as per Section 5.1.3 in case of cardiac failure
- [i] Applicable to women of childbearing potential (premenopausal or less than 12 months of amenorrhea post-menopause, and who have not undergone surgical sterilization); a serum pregnancy test needs to be completed within 7 days prior to the first dose of first administration of the protocol required chemotherapy treatment. Testing should be repeated every 3 months for the duration of study treatment and until at least 7 months after the last dose of study treatment. Any positive urine pregnancy test needs to be confirmed by serum pregnancy test. Additional pregnancy testing should be completed as clinically indicated for the duration of study treatment and until at least 7 months after the last dose of study treatment. Any positive urine pregnancy test needs to be confirmed by serum pregnancy test.
- [j] Hematology: hemoglobin, white blood cells (WBC) and differential, absolute neutrophil count (ANC), platelet count. Biochemistry: creatinine, urea (BUN), SGPT (ALT), SGOT (AST), total bilirubin, alkaline phosphatase, glycaemia, albumin, sodium, potassium and calcium. Additional hematology and biochemistry tests may be performed as per institutional practice, but these data will not be collected

[k] American Society of Clinical Oncology (ASCO) 2006 Guideline for Breast Cancer Follow-up in the adjuvant setting (Khatcheressian et al. 2006). In brief:

History/physical examination - every 3 to 6 months for the first 3 years after primary therapy; every 6 to 12 months for years 4 and 5, then annually.

Mammography - first post-treatment mammogram 1 year after the initial mammogram that leads to diagnosis, but no earlier than 6 months after definitive radiation therapy. Subsequent mammograms should be obtained as indicated for surveillance of abnormalities.

Pelvic examination - regular gynecologic follow-up is recommended for all women. Patients who receive tamoxifen should be advised to report any vaginal bleeding to their physicians.

The following are not recommended for routine surveillance: Routine blood tests (full blood counts and liver function tests), imaging studies (chest x-ray, bone Scans, liver ultrasound, CT Scans, FDG-PET Scans, and breast MRI), tumor marker assessments (CA 15-3, CA 27.29, and CEA)

In neoadjuvant setting mammogram and ultrasound have to be performed at Screening and before surgery. After first sequence comprehensive of Anthracycline (4 cycles, on day 1 of first cycle of subsequent sequence) the mammogram is optional.

[l] After informed consent, but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention will be collected. Before study closure, all AEs/SAEs will be reported regardless of the study drug relationship. After study closure, all SAEs will be reported indefinitely regardless relationship to the drug. NCI-CTCAE version 4 should be used for AE coding. All SAEs, and AEs that are not resolved after the end of study, should be followed-up until resolution. See section 5.3.1 for AEs reporting period.

[m] All concomitant medications and prior treatments for BC must be reported in the eCRF starting at the Screening visit. The year of start and end date (when applicable) of the past and current concomitant treatments for BC, as well as the route and dose, will be collected when available. All concomitant medication will be recorded between the Screening and the Safety Follow-up visits. Thereafter, only medication applicable for long-term reporting must be reported, including: breast cancer treatments (e.g., hormonal therapy), anti-cancer treatments given to treat a recurrence, medications related to the treatment of SAEs that are applicable for long-term reporting (e.g., treatment of heart failure)

[n] Trastuzumab is administered subcutaneously at a fixed dose of 600 mg, 3-weekly for a total of at least 18 cycles/1 year (regardless of body weight) starting after first chemotherapy sequence based on anthracycline (4 cycles).

[o] Pathological Response assessment to be performed using the resected tumor according to guidelines provided

[p] Approximately 3-monthly (every 4 cycles) refers to pre-study treatment administration at: Cycle 5 (after 4 cycles of anthracycline based chemotherapy), Cycle 9 (after 4 cycles of taxane based chemotherapy plus trastuzumab SC), Cycles 13, 17 and 21 and at safety follow-up visit (4 weeks after last study treatment). Cardiac assessments at follow-up visits have to be performed at 6, 12, 18 and 24 months following treatment cessation.

[q] Patients will undergo a Safety Follow-up visit 4 weeks after their last dose of study treatment

\* Local Blood samples will be obtained at the following time points:

Adjuvant:

1. basal (Day 1-7);
2. after first sequence comprehensive of Anthracycline containing regimens (on Day 1 of first cycle of Taxane + trastuzumab SC administration)
3. end of chemotherapy treatment (on Day 1 of C 5 before starting administration of Trastuzumab alone)

Neoadjuvant:

- 1 basal (Day 1-7);
- 2 after first sequence comprehensive of Anthracycline containing regimens (on Day 1 of first cycle of Taxane + trastuzumab SC administration)
- 3 end of chemotherapy treatment (8 cycles, on Day 1 of first cycle of subsequent sequence)

\* \*Local: Tissue samples will be obtained at the following points:

Neoadjuvant:

- basal (Day 1-7);
- at surgery

Adjuvant:

- at surgery

## **APPENDIX 2**

### **Algorithm for continuation and discontinuation of trastuzumab SC or IV based on LVEF assessment in asymptomatic patients**

### **Appendix 3**

#### **The conventional doses of the selected regimens Chemotherapy Agents**

EC: Epirubicin 90 mg/m<sup>2</sup>  
Cyclophosphamide, 600 mg/m<sup>2</sup>

AC: Doxorubicin, 60 mg/m<sup>2</sup>  
Cyclophosphamide, 600 mg/m<sup>2</sup>

Docetaxel, 100 mg/m<sup>2</sup> 1 hour infusion every 3 weeks

Docetaxel, 75 mg/m<sup>2</sup> 1 hour infusion every 3 weeks

Paclitaxel, 80 mg/m<sup>2</sup> 1 hour infusion every one week

FAC: Fluorouracil, 600 mg/m<sup>2</sup>  
Doxorubicin, 60 mg/m<sup>2</sup>  
Cyclophosphamide, 600 mg/m<sup>2</sup>  
Iv bolus every 3 weeks

FEC: Fluorouracil, 600 mg/m<sup>2</sup>  
Epirubicin, 90 mg/m<sup>2</sup>  
Cyclophosphamide, 600 mg/m<sup>2</sup>  
IV bolus every 3 weeks



## Appendix4

### NYHA Classification and Left Ventricular Systolic Dysfunction NCI CTCAE version 4.0 Grading

Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or angina pain.
Class II	Patients with cardiac disease resulting in slight limitations of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitations of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea or anginal pain
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
Oxford textbook of internal medicine. Vol 2, pp 2228. Oxford University Press. 1997	

## APPENDIX 5

### Single-use Injection Device (SID) Satisfaction Questionnaire Studio ML 28879

The SID Satisfaction Questionnaire has to be completed by patients in **Cohort B** who completed a minimum of 14 administrations of trastuzumab SC using SID, at least 10 self-administered

Site number: \_\_\_\_\_ Date: \_\_\_\_\_

Patient number: \_\_\_\_\_

*Please rate your level of agreement or disagreement with each the following statements, by placing an "X" in the appropriate box (one answer for each statement):*

- 1 Following the first injection given by the physician/nurse and training on how to use the SID, I felt comfortable injecting the study drug by myself.**

☐<sub>1</sub> Strongly Disagree      ☐<sub>2</sub> Disagree      ☐<sub>3</sub> Unsure      ☐<sub>4</sub> Agree      ☐<sub>5</sub> Strongly agree

- 2 The SID was convenient and easy to use.**

☐<sub>1</sub> Strongly Disagree      ☐<sub>2</sub> Disagree      ☐<sub>3</sub> Unsure      ☐<sub>4</sub> Agree      ☐<sub>5</sub> Strongly agree

- 3 I am confident giving myself an injection in the thigh with the SID.**

☐<sub>1</sub> Strongly Disagree      ☐<sub>2</sub> Disagree      ☐<sub>3</sub> Unsure      ☐<sub>4</sub> Agree      ☐<sub>5</sub> Strongly agree

- 4 Taking all things into account, I find self-administration using the SID satisfactory.**

☐<sub>1</sub> Strongly Disagree      ☐<sub>2</sub> Disagree      ☐<sub>3</sub> Unsure      ☐<sub>4</sub> Agree      ☐<sub>5</sub> Strongly agree

- 5 If given the opportunity, I would choose to continue self-injecting the study drug using the SID at home.**

☐<sub>1</sub> Strongly Disagree      ☐<sub>2</sub> Disagree      ☐<sub>3</sub> Unsure      ☐<sub>4</sub> Agree      ☐<sub>5</sub> Strongly agree

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